ANNALS of ALLERGY

Published by

The American College of Allergists

VOLUME 9

January through December, 1951

Contents for January-February, 1951

Contents for March-April, 1951

Contents for May-June, 1951

Contents for July-August, 1951

Contents for September-October, 1951

Contents for November-December, 1951

ANNALS of ALLERGY

Published by
The American College of Allergists

Volume 9 January-February, 1951 Number 1

ADRENOCORTICOTROPIC HORMONE (ACTH); ITS EFFECT IN ATOPIC DERMATITIS

THERON G. RANDOLPH, M.D., F.A.C.A., and JOHN P. ROLLINS, M.D.
Chicago, Illinois

THE beneficial effects of adrenocorticotropic hormone (ACTH) in bronchial asthma, ragweed hay fever, and other allergic disturbances[1,2,8,10,13] prompted a study of its effect in atopic dermatitis. Brief reference to the response of two cases of atopic dermatitis treated with ACTH has previously been made.[10] Our aim in this presentation is to give a more detailed report of these as well as of two other cases in which similar observations have been made.

These cases were selected on the basis of their typical acute dermatitis which had failed to respond completely to prolonged specific allergic diagnosis and management. However, in each instance acute accentuations of the dermatitis could be induced at will following the ingestion of one or more known allergenic foods.

Each patient was hospitalized for at least three days prior to starting therapy with ACTH. Serial eosinophil and differential blood counts were performed with the direct counting chamber glycol stain technique[5] prior to, during, and following the administration of ACTH.

Case 1.—D.B., aged thirty-one, was first seen in October, 1948, at which time he presented an extensive area of dermatitis in each antecubital space measuring 4 by 6 inches in diameter and similar involvement of the entire anterior neck extending over the clavicles laterally. These involved areas were acutely inflamed, with extensive lichenification and unmistakable evidence of excoriation resulting from scratching. He gave a history of having had some dermatitis of these areas since infancy, with a tendency for increased involvement during the ragweed pollinating season coincident with ragweed hay fever which had been present for the past decade. He had also been subject to perennial nasal allergy for fifteen years; this was characterized by an accentuation of symptoms in the early morning hours and a marked intolerance

Presented at the Sixth Annual Meeting of The American College of Allergists, January 15-18, St. Louis, Missouri.
Dr. Randolph is instructor in internal medicine, Northwestern University Medical School.
Dr. Rollins is research fellow in internal medicine, Northwestern University Medical School.

to drafts. Attacks of asthma had occurred during the height of the 1943 and 1949 ragweed seasons.

For a period of six months prior to his initial visit he had also complained of pulling and drawing sensations across his shoulders and in the muscles of the posterior neck.[3] Although these symptoms did not occur in association with head pain, he had remained subject to intermittent headaches associated with nausea occurring on the average of once monthly for many years. He also complained of chronic insomnia, having difficulty in getting to sleep on retiring and being characteristically awakened from sleep two or three times during the night; at these times he would thrash about in bed, complaining of tired, restless legs and inability to return to sleep. These symptoms had also been associated with chronic fatigue of many years' duration, unaccountably worse certain days than others, accentuated in the morning on arising and again immediately after the noon meal. He fell asleep each evening between 7:00 and 8:00 p.m., his evening somnolence precluding the possibility of performing any serious work in the evenings. This chronic fatigue materially interfered with his comprehension in reading and general working ability both as a student and subsequently as a teacher in a private school. These typical allergic symptoms have been described previously.[6,14]

The ingestion of alcoholic beverages, particularly beer and whiskey, was known to accentuate the dermatitis but he was not aware of other causative factors. Abstaining from alcoholic drinks for months at a time failed to change the course of his dermatitis or other allergic manifestations.

Although found to be ragweed sensitive, there was no other evidence of inhalant allergy as determined from the details of his history or as a result of skin testing.

An individual food test[12] with wheat was performed October 30, 1948. During the third day of the four-day period of wheat avoidance prior to the test he noted a marked improvement in both the nasal symptoms and the dermatitis; this was manifested by a subsidence of sneezing and pruritus with blanching of the erythematous skin lesions. The experimental feeding of whole wheat cereal at 1:00 p.m. and a second smaller feeding an hour later were followed by a recurrence of pruritus at 11:00 p.m., localized to the involved skin sites. This discomfort was more marked than any he had experienced in the two preceding days. By the following morning there was an acute accentuation of the dermatitis with evidence of increased erythema and recent excoriations.

After ten days of complete wheat avoidance the involved areas were free of residual erythema. With the continuation of this dietary program he had no further recurrences of his dermatitis for several months. He also obtained complete relief of his nuchal myalgia, insomnia, restless legs, chronic nasal symptoms and intermittent headaches.

In April, 1949, wheat was returned to his diet in a single feeding once a week and was tolerated for several weeks on this schedule. In May he began eating wheat once daily in the noon meal. After two weeks of this schedule he developed a progressive dermatitis of the antecubital areas, the pruritus of which was most troublesome between 7:00 and 10:00 p.m. nightly. He then avoided wheat completely and remained free of dermatitis for the following two months.

He returned wheat to his diet in mid-July, 1949, and noted a recurrence of antecubital eczema within a few days. When seen at the end of this six-week period, he had extensive areas of acute dermatitis in the antecubital regions as well as over the anterior neck. He also had had hay fever and one severe attack of asthma during the height of the ragweed pollinating period. The absolute avoidance of wheat was begun September 1. The dermatitis showed progressive clearing on this schedule in spite of sustained high ragweed pollen counts and continuing severe daily hay fever.

His individual food test with wheat was repeated September 9, 1949, two days before starting therapy with ACTH, as illustrated by the sudden fluctuations of the

blood counts at the extreme left of Figure 1. Eight minutes after the experimental ingestion of wheat he developed marked pallor; this was followed by drowsiness at twelve minutes and progressive nasal stuffiness beginning at twenty-five minutes. He noticed the onset of itching of the antecubital areas and the anterior neck fifty

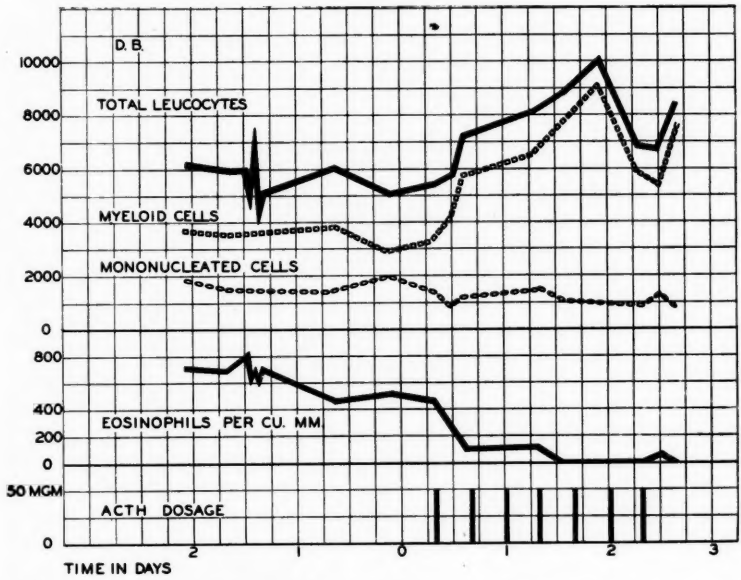


Fig. 1. Variations in the peripheral blood cells following the ingestion of an allergenic food, wheat, in D. B. prior to ACTH therapy to the left and changes in the peripheral blood elements coincident with the administration of ACTH to the right.

minutes after the wheat feeding and was subsequently observed scratching these areas. His nasal stuffiness and pruritus became sharply accentuated immediately after the second feeding of wheat, given an hour after the initial serving; this was followed by a deep stuporous sleep from which it was difficult to awaken him. Severe pruritus of the areas previously involved by the dermatitis continued throughout the night. He was hospitalized that evening and mild shortness of breath and wheezing as well as marked nasal stuffiness and pruritus continued through the following day. Wheat was purposely continued in his diet in three feedings per day. By the third day he had developed a maximum degree of dermatitis, characterized by acute oozing skin lesions of the involved areas.

At this time he was started on adrenocorticotropic hormone (ACTH), receiving a total dosage of 350 mg intramuscularly in a period of three days, wheat being continued in the diet. Within three hours after the initial injection of 50 mg he noticed a decrease in the itching of his arms and neck and decreased nasal stuffiness. By the end of five hours the pruritus had completely subsided. A noticeable subsidence of erythema and absence of acute oozing lesions as well as peripheral healing of denuded areas were evident at twenty-four hours. Although he continued to ingest wheat three times daily, there was a sustained improvement in his dermatitis for a week after the cessation of ACTH therapy. At the completion of this period of hormone treatment he noticed complete relief of his usual afternoon drowsiness and

fatigue. He also commented spontaneously on the occurrence of a general sense of well being, calmness, and relaxation as well as a striking increase in his ability to concentrate and to read comprehendingly.

However, a week after the cessation of ACTH therapy he experienced a rapidly

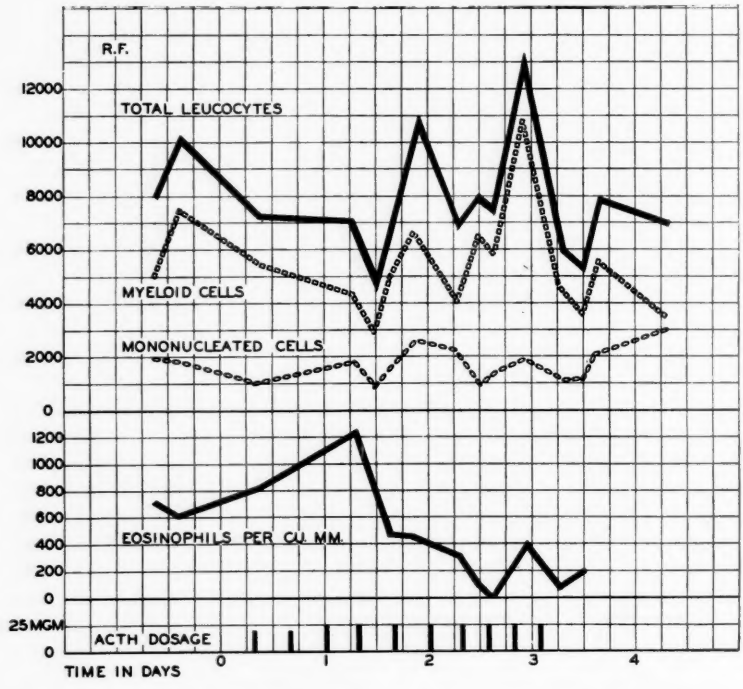


Fig. 2. Variations in the peripheral blood cells in R. F., six years of age, during treatment with ACTH.

progressive recurrence of his dermatitis which within a period of another week reached a degree of severity and an extent of involvement greater than that observed on any previous occasion. Coincident with the onset of this recurrence he immediately returned to his formerly restricted diet, but in spite of this measure his dermatitis continued unabated for the following three weeks. At this point another type of treatment was started which will be reported subsequently.

Case 2.—R.F., a boy six years of age, had been subject to generalized atopic dermatitis since infancy. He had obtained approximately 80 per cent relief of his dermatitis during the past year as a result of the avoidance of corn and specific therapy with house dust and *Alternaria.* On repeated occasions the test or inadvertent ingestion of corn meal or such refined products as cornstarch or corn sugar[4,11] was followed by immediate acute recurrences of his skin lesions. The eczema also became accentuated after the inhalation of the fumes of pop corn machines and each time that he played shuffleboard where cornstarch had previously been applied to the floor.

For a period of three months before beginning treatment with ACTH he had had a progressive increase in his dermatitis proved to be due at least in part to the acquisition of sensitivity to wheat and cane sugar. However, the avoidance of incriminated foods and the maintenance of specific inhalant therapy (house dust) did not effect complete relief of his dermatitis.

The child was hospitalized and placed on a general diet, including corn, in some form, three times daily; this program was followed by a rapidly progressive generalized dermatitis. A prompt improvement of the skin, as manifested by cessation of pruritus and progressive clearing of the erythematous, oozing skin lesions, occurred coincident with a course of ACTH injections consisting of 16.6 mg every eight hours for the first day, 25.0 mg every eight hours for the second day and every six hours for the third day, resulting in a total dosage of 225.0 mg. This improvement occurred despite the continued ingestion of corn products and other food allergens during the treatment period. The changes in the eosinophils and other peripheral blood elements are illustrated in Figure 2.

In this case specific allergenic foods were avoided coincident with the cessation of ACTH therapy. He continued without troublesome symptoms for the following ten days but then reverted to a greater degree of involvement than existed prior to starting these observations. Severe generalized dermatitis continued for the next several weeks in spite of specific allergic management; he then gradually improved and after three weeks reached approximately the same clinical condition as existed prior to initiating ACTH therapy.

Case 3.—M.N., a girl six years of age, gave a history of generalized dermatitis since infancy. She had no other allergic manifestations with the exception of occasional attacks of bronchitis.

Her history was positive for sensitization to chicken and eggs; the ingestion of either was known to cause an accentuation of her dermatitis as well as swelling of her eyes. Allergic investigation prior to starting therapy with ACTH revealed a high degree of sensitivity to milk in that its experimental ingestion was followed by a sharp increase in her dermatitis. She was found to be somewhat less sensitive to wheat and oats as a result of individual food tests with these foods.

The avoidance of known allergenic foods was only partially effective in relieving her eczema. The status of her dermatitis prior to hospitalization for ACTH therapy is shown in Figure 3. Upon admission to the hospital she was placed on her restricted diet with the exception that oats and milk were allowed freely. Her chronic dermatitis entered an acute phase within twenty-four hours from the time these foods were introduced to her diet; this degree of involvement is illustrated in Figure 4.

ACTH therapy was started on the fifth day of this diet; a total of 200.0 mg was administered intramuscularly in divided doses during a period of three days. Her previously existing acute dermatitis subsided during the course of treatment; the pruritus ceased during the first twenty-four hours; a progressive decrease of the erythema and healing of open lesions continued during the course of treatment and for a period of four days after stopping hormone therapy. Maximum improvement of her skin is shown in Figure 5. By the end of a week after ACTH was discontinued, her dermatitis had recurred in its former degree of severity which existed immediately prior to therapy. At this time she was returned to her formerly restricted diet, upon which she showed approximately 50 per cent improvement; this was about the same degree of skin involvement as existed prior to starting treatment with ACTH.

Case 4.—R.D., a well-nourished boy, aged three and one-half years, had been subject to extensive atopic dermatitis since the age of one week, and a chronic stuffy

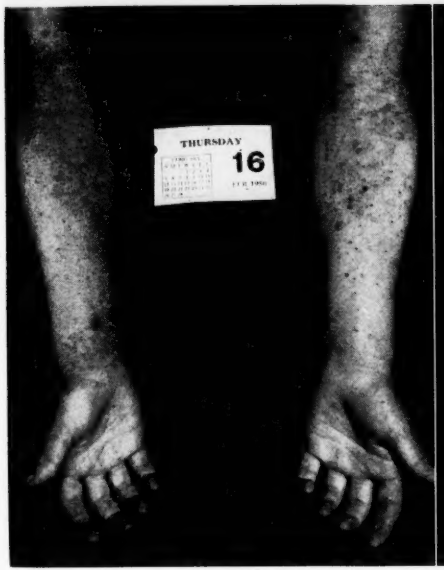


Fig. 3. Condition of the dermatitis of the arms prior to the ingestion of allergenic foods in M. N., a child six years of age.

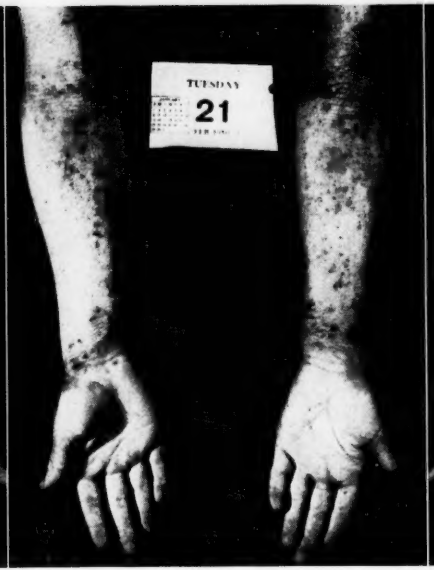


Fig. 4. Condition of the dermatitis of the arms twenty-four hours after returning milk and oats to the diet of M. N.

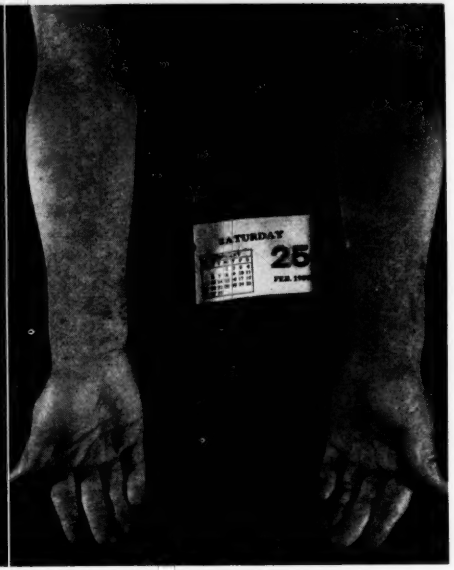


Fig. 5. Maximum improvement of the skin in case M. N. after therapy with ACTH even though known food allergens were continued in the diet.

nose and intermittent headaches for the past six months prior to his initial visit in March, 1950. At this time his dermatitis was generalized and acutely erythematous in character with the most severe degree of involvement limited to his face. The ingestion of peaches and chocolate was known to be followed by an accentuation of his skin lesions.

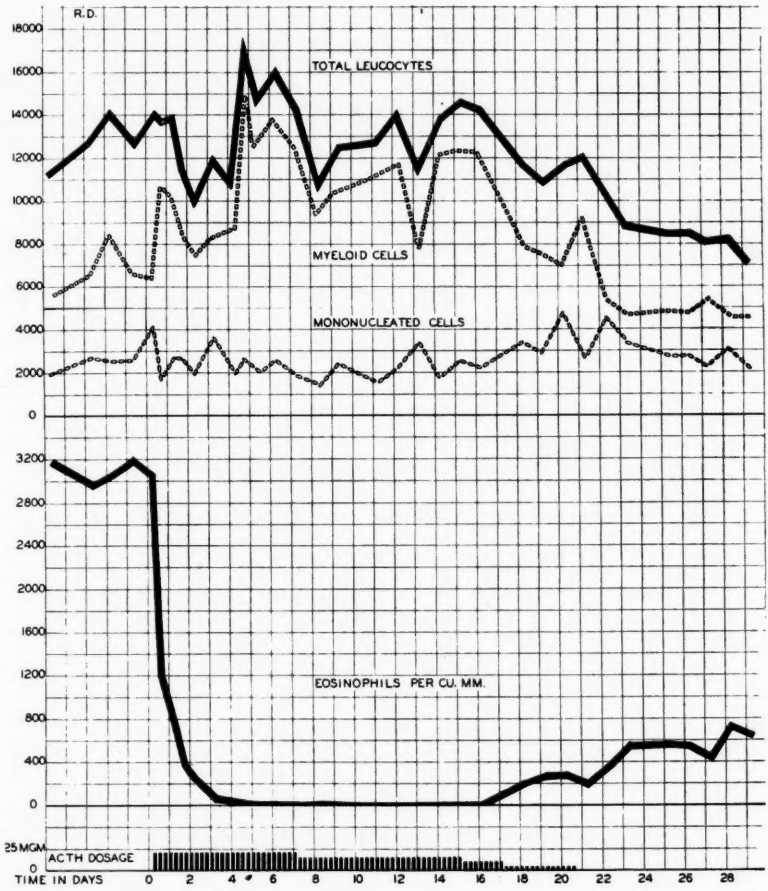


Fig. 6. Variations in the peripheral blood elements coincident with the administration of ACTH in R. D., a child three and one-half years of age.

He was found to be house dust sensitive as a result of performing intradermal skin tests with serial dilutions of house dust extract according to the technique recently described.[7] Specific therapy with house dust in accordance with these schedules[7] and with doses materially below his titrated degree of skin test sensitivity failed to change the course of his allergic symptoms. House dust therapy was continued during the following period of six weeks, during which time an attempt was made to diagnose specific food sensitivity. Although there was suggestive evidence that the

Fig. 7. Status of the dermatitis of the face in R. D. immediately prior to the administration of ACTH.

Fig. 8. Improvement in the dermatitis of R. D. began twenty-four hours after starting treatment with ACTH and reached the maximum degree of improvement at the end of the third week of therapy.

Fig. 9. A recurrence of vesicular lesions of the face occurred two days after the cessation of ACTH treatment in R. D., reaching the degree of involvement as illustrated here at the end of a week. By the end of two weeks he had reverted to the condition existing prior to starting treatment with ACTH.

experimental ingestion of potatoes and wheat resulted in a flare of his dermatitis, he did not improve with the avoidance of these articles of the diet as well as peaches and chocolate suspected on the basis of evidence obtained from the history. Individual food tests with all other major foods were not associated with an apparent accentuation of symptoms, though this was difficult to ascertain with accuracy because of the continued severity of his skin lesions.

There being no obvious improvement in his dermatitis as a result of these measures as well as from adherence to various types of basic elimination diets, he was hospitalized April 28 in preparation for therapy with ACTH. His diet immediately prior to hospital admission had omitted wheat, potatoes, peaches and chocolate; this was continued throughout the period of hospital observation. He received no therapy during the pre-treatment hospital period other than the continued use of vaseline locally and the performance of an epinephrine test on the second day. An eosinophil count of 3,146 and a total leukocyte count of 11,600 per cu mm of blood, immediately prior to the injection of 0.2 cc epinephrine, decreased rapidly after the injection and reached the lowest values recorded two hours and fifteen minutes later: namely, 1,562 eosinophils and 10,050 total leukocytes. Aside from the blood determinations in this epinephrine test, variations in the total and differential leukocyte counts are illustrated in Figure 6. One should note particularly the striking diminution of eosinophils coincident with the first few days of ACTH therapy.

The status of his facial dermatitis immediately prior to the institution of ACTH therapy is illustrated in Figure 7. As in the other cases, this patient exhibited a striking clinical improvement beginning within twenty-four hours after the institution of therapy, the maximum degree of which is illustrated in the photograph taken May 24 at the end of the third week of continuous treatment, as illustrated in Figure 8. He received a total of 1,080 mg ACTH. A dosage of 20 mg was injected intramuscularly every six hours for the first week; this was followed by subsequent reductions in dosage to 12.0, 9.25 and 3.25 mg, as shown graphically in Figure 6.

The first evidence of the recurrence of erythematous, vesicular lesions of his face was noted at the end of the second day after stopping treatment. At the time of his discharge from the hospital June 2, 1950, he again had extensive areas of dermatitis, as shown in Figure 9. It is interesting, however, that at this time or for the subsequent week after returning home there was no obvious evidence of pruritus, as shown by the absence of itching and excoriations. There was a very rapid recurrence of acute dermatitis during the second week at home; this reached such an acute phase that it was necessary to rehospitalize the patient. His condition at that time, June 16, was approximately the same as shown in the photograph taken prior to the onset of ACTH therapy (Figure 7).

DISCUSSION AND SUMMARY

ACTH is an effective therapeutic agent in chronic atopic dermatitis.

The first three patients in this series were hospitalized, and acute exacerbations of their dermatitis were induced experimentally following the deliberate ingestion of foods to which they were known to be specifically sensitized. Although allergenic foods were continued in the respective diets of these individuals, each showed a rapid and progressive clearing of the lesions of atopic dermatitis during short courses of ACTH therapy; this degree of improvement persisted for a period of four or five days following the cessation of treatment with ACTH, in two of the patients in whom allergenic foods were continued in the diet. Another patient (R.F.) was managed similarly with the exception that his specific foods were with-

drawn from the diet coincident with the cessation of ACTH therapy; his clinical improvement persisted for a period of ten days prior to the recurrence of severe dermatitis. The fourth patient (R.D.), less completely diagnosed from the standpoint of specific food allergy than the other three, was treated with ACTH for a period of three weeks; during the latter part of this interval the dosage of ACTH was gradually reduced. Although he was maintained on a constant diet throughout the entire period of observation, his dermatitis recurred two days after the cessation of therapy, but the recurrence was less abrupt and was characterized by a relative absence of pruritus during the first ten days of gradually recurring eczema.

Each patient had a recurrence of dermatitis following the cessation of ACTH therapy, at least as severe and in some instances more acute, than that present for several weeks prior to the institution of treatment with ACTH. This degree of involvement persisted from one to three weeks and then reverted to the approximate status existing prior to starting hormone treatment.

It is of interest that, in general, patients with atopic dermatitis require a higher daily dose of ACTH in order to effect the expected degree of eosinopenia[9] and clinical improvement than determined for other allergic syndromes thus far treated.[8,10] This finding does not appear to be related to the age of the patient.

As in other allergic individuals treated with short courses of adrenocorticotropic hormone (ACTH),[8,10] deleterious effects from this therapy have not been noted. In the final case of this series in which treatment was continued at relatively high levels of dosage (considering the patient's age of three years), moderate fluid retention and general sluggishness occurred at the end of the first week of treatment, but with a reduction in dosage his weight and behavior returned to their previous status.

In general, the results of treatment with ACTH in atopic dermatitis are not as good as in cases of hay fever and bronchial asthma in respect to the duration of relief of symptoms following short courses of this therapy. Observations are now in progress to determine the minimum effective dose of this hormone which will maintain the beneficial effects induced as a result of short courses of ACTH therapy. It is possible that longer periods of treatment might be more effective in bringing about a more prolonged period of relief of symptoms of atopic dermatitis, although this desired result did not occur in the one instance in which therapy was continued for a period of three weeks.

REFERENCES

1. Bordley, J. E.; Carey, R. A.; Harvey, A. McG.; Howard, J. E.; Kattus, A. A.; Newman, E. V., and Winkenwerder, W. W.: Preliminary observations on the effect of adrenocorticotropic hormone (ACTH) in allergic diseases. Bull. Johns Hopkins Hosp., 85:396, 1949.
2. Howard, J. E.: Preliminary report on the results of ACTH in the hypersensitive states. Proc. First ACTH Conference. Philadelphia: The Blakiston Co., 1950.

(Continued on Page 18)

CLINICAL OBSERVATIONS ON THE EFFECTIVENESS OF A COMBINATION OF AN ANTIHISTADINE DECARBOXYLASE AND AN ANTIHISTAMINE

Preliminary Report

LIVINGSTON CHUNN, M.D.
Philadelphia, Pennsylvania

BECAUSE of the well-known limitations of the antihistaminic drugs, any new approach to a resolution of the problem seems worthy of clinical investigation. The concept of the antihistidine decarboxylase is new. Chemicals effective in controlling the activity of histidine decarboxylase should be active in preventing the formation of histamine. This approach was deemed more logical than that of the pharmacological counteraction of histamine once formed. It would, however, seem advisable to include an agent of the standard antihistamine type to combat formed histamine.

The agent used as an antihistidine decarboxylase is d-catechin, which has been demonstrated by Martin et al[3] to produce *in vitro* a 60 per cent inhibition of histidine decarboxylase at a concentration of 0.1 mg/cc. *In vivo* in doses of 5 mg per kilogram intraperitoneally, d-catechin prevented the development of anaphylactic shock in guinea pigs.[4] The antihistamine selected for use was dimethylamino-propylphenothiazine, which has been stated to be some seven times as powerful as mepyramine maleate.[1]

The combination (NDR-112) used consisted of 25 mg of dimethylamino-propylphenothiazine and 125 mg of d-catechin per tablet.* The dosage was four tablets daily. In children, one tablet was given each day. This dosage was arbitrarily selected to check incidence of side effects and is probably far in excess of minimal dosage for optimal effect.

ECZEMA

Ten cases of eczema were treated for periods ranging from seven to thirty-one days; locally, an olive oil emulsion was used in all cases. No appreciable improvement was observed in any of the ten cases (Table I). Two patients (Cases 5 and 8) complained of drowsiness as a side reaction.

Case 5.—Mrs. B.S., aged twenty-six, a white woman, was first seen on November 17, 1949, with itching, scaling, fissured lesions on both hands, and itching, scaling, ill-defined, erythematous lesions on her forearms. She stated that she had had a rash since she was seventeen years of age, and that she had never been free of the rash since it first broke out nine years ago, although she had numerous and various forms of treatment, including x-ray therapy. No history of allergy was elicited. The diagnosis was eczema, and the treatment consisted of NDR-112 tablets—one tablet orally four times a day—and olive oil emulsion locally.

The patient was next seen on November 29, twelve days later. No improvement was observed, and the patient still complained of severe itching. She stated that two days after she started to take the medicine, she seemed to feel sleepy all day long

*Supplied by Medical Research Division of The National Drug Company, Philadelphia, Pennsylvania.

TABLE I. ECZEMA

Case	Sex	Age	Duration of Condition	Total Days of Treatment	Result	Side Reaction
1	F	32 years	11 years	31 days	No improvement	None
2	M	52 years	1 year	24 days	No improvement	None
3	F	33 years	18 months	28 days	No improvement	None
4	F	21 years	2 years	13 days	No improvement	None
5	F	26 years	9 years	9 days	No improvement	Drowsiness
6	F	11 years	2 years	11 days	No improvement	None
7	F	39 years	20 years	22 days	No improvement	None
8	F	58 years	2 years	5 days	No improvement	Drowsiness
9	M	24 years	3 years	16 days	No improvement	None
10	M	58 years	7 months	7 days	No improvement	None

TABLE II. CONTACT DERMATITIS

Case	Sex	Age	Duration of Condition	Total Days of Treatment	Result	Side Reaction
1	F	20 years	3 weeks	14 days	No improvement	None
2	M	43 years	1 week	17 days	No improvement	None
3	M	68 years	2 weeks	27 days	No improvement	None
4	F	52 years	6 weeks	22 days	No improvement	None
5	F	59 years	5 weeks	20 days	No improvement	None
6	M	51 years	2 weeks	22 days	No improvement	None
7	M	60 years	2 weeks	11 days	No improvement	None
8	F	25 years	8 weeks	25 days	No improvement	None

TABLE III. ATOPIC DERMATITIS

Case	Sex	Age	Duration of Condition	Total Days of Treatment	Result	Side Reaction
1	F	2 years	14 months	14 days	No improvement	None
2	F	12 years	11 years	14 days	No improvement	None
3	M	4 years	2 years	13 days	No improvement	None

and had no ambition to do anything around the house. She continued to take the tablets for six or seven more days and then stopped because she felt that they were making her sleepy and that they were not helping her skin condition at all. She stated that she had not been sleepy ever since she stopped taking the pills. The oral medication was stopped, and she was managed with local applications of a soothing ointment only.

Case 8.—Mrs. L.T., a white woman, aged fifty-eight, was first seen on November 16, 1949. She complained of an itching, scaling rash on the hands, the bends of the elbows, the lips and the chest. She stated that she had had the rash for two years, and that she had been treated by several doctors, but no one had helped her. The diagnosis of her condition was eczema, and the treatment consisted of one tablet of NDR-112 four times a day, and olive oil emulsion locally.

The patient was again seen on November 24, eight days later. No improvement was observed. She stated that when she was taking the medicine, she felt so drowsy that she had stopped taking the pills about three days previously. This patient, however, was encouraged to continue with the medication.

On December 17 this patient was again seen. She stated that she took the pills for several days but she stopped because she again had the drowsy feeling when she took the medicine. She was unimproved.

TABLE IV. URTICARIA

Case	Sex	Age	Duration of Condition	Total Days of Treatment	Result	Side Reaction
1	M	56 years	2 days	7 days	Itching subsided, skin is clear	None
2	F	23 years	1 day	8 days	Itching subsided, skin is clear	None
3	M	2 years	1 day	6 days	Itching subsided, skin is clear	None
4	M	43 years	1 day	5 days	Itching subsided, skin is clear	None
5	M	56 years	2 days	5 days	Itching subsided, skin is clear	None
6	F	43 years	1 day	2 days	Itching subsided. Occasional wheal still present	None

TABLE V. COMMON COLD

Case	Sex	Age	Duration of Condition	Total Days of Treatment	Result	Side Reaction
1	F	40 years	3 days	4 days	Improved	None
2	M	44 years	7 days	5 days	Complete relief of symptoms	None
3	M	57 years	2 days	5 days	Complete relief of symptoms	None
4	M	40 years	2 days	4 days	Improved	None
5	M	55 years	14 days	6 days	Improved	None
6	F	27 years	5 days	10 days	Not improved	None
7	M	42 years	2 days	5 days	Complete relief of symptoms	None
8	M	54 years	2 days	5 days	Complete relief of symptoms	None
9	M	30 years	2 days	5 days	Complete relief of symptoms	None
10	F	34 years	2 days	7 days	Improved	None
11	M	19 years	7 days	Did not return for further observation		
12	M	36 years	6 days	Did not return for further observation		
13	M	20 years	7 days	Did not return for further observation		
14	M	67 years	2 days	Did not return for further observation		
15	F		2 days	Did not return for further observation		
16	M	50 years	3 days	Did not return for further observation		
17	M	41 years	10 days	Did not return for further observation		
18	M	63 years	7 days	Did not return for further observation		
19	M	48 years	3 days	Did not return for further observation		
20	M	70 years	3 days	Did not return for further observation		
21	M	47 years	14 days	Did not return for further observation		
22	M	40 years	14 days	Did not return for further observation		
23	M	68 years	2 days	Did not return for further observation		
				Did not return for further observation		

CONTACT DERMATITIS

Eight cases of contact dermatitis were treated and observed for periods ranging from eleven to twenty-five days (Table II). Locally, these patients were managed with olive oil emulsion. No appreciable improvement was seen in any of the eight cases, and none presented any evidence of a side reaction from the antihistaminic (NDR-112) tablets.

ATOPIC DERMATITIS

Three cases of atopic dermatitis were treated with no improvement of skin lesions (Table III). These three cases were all children, aged two, twelve, and four years. The two younger children were given only one tablet of NDR-112 daily. The local treatment consisted of application of olive oil emulsion to affected areas three times daily. No side reaction was observed in any of these three cases.

URTICARIA

Six cases of acute urticaria from various causes were treated with the antihistaminic tablets (Table IV); no local treatment was prescribed for any of these cases. Case 3, a child of two years, was given only one tablet daily; the remaining five patients took four tablets a day. All, except

Case 6, were relieved of their itching and rash in from five to eight days. Case 6, seen two days after treatment was started, was relieved of her itching, but she still witnessed occasional outbreak of wheals. She did not return for further observation. No side reaction was observed in any of these six cases.

COMMON COLD

A total of twenty-three cases of common cold were treated (Table V). Each patient was instructed to take one NDR-112 tablet four times a day and to return in four days. Ten patients returned for further observations, but thirteen cases failed to return at all and it is probable that they were cured. Of the ten patients who returned, five cases were completely alleviated of their symptoms, four cases were improved, and only one case showed no improvement at all. The unimproved patient subsequently developed a chest complication which was treated with antibiotics. No side reaction was observed in any of these cases.

DISCUSSION

Halpern[2] has reported a 25 per cent incidence of drowsiness following dosages of 100 mg daily of dimethylaminopropylphenothiazine. In our series of thirty-seven patients receiving NDR-112 only two showed drowsiness as a side reaction, representing approximately 6 per cent. This reduced incidence of drowsiness may well be due to the simultaneous administration of d-catechin. It is to be noted that the general incidence of side reaction, specifically drowsiness, seen with antihistamines varies from 15 to 56 per cent.[6]

NDR-112 was ineffective in eczema, contact dermatitis, and atopic dermatitis. This finding is in agreement with that of Shulman[5] and Halpern,[6] who used dimethylaminopropylphenothiazine alone. In urticaria, five out of six patients responded. Here, again, the observation is in agreement with Shulman,[5] who reported eight cases of urticaria with 100 per cent response, and that of Halpern,[6] who reported 88 per cent response to treatment with dimethylaminopropylphenothiazine. The literature does not disclose any report on the use of the phenothiazine compound in the common cold. While our series is too small for other than a preliminary comment, it would seem that approximately 90 per cent were completely relieved or experienced improvement as reflected in symptoms of the common cold.

SUMMARY

A combination of an antihistidine decarboxylase (d-catechin) and an antihistamine (dimethylaminopropylphenothiazine) failed to produce beneficial effects in eczema or in contact or atopic dermatitis. In urticaria, the drugs were effective in completely alleviating the conditions in 83 per cent in five to eight days. In patients with common cold, 90 per cent were completely relieved of symptoms or improved by this treatment.

(Continued on Page 128)

THERAPEUTIC EFFECTS OF AN ANTIHISTADINE DECARBOXYLASE AND ANTIHISTAMINE COMBINATION

JULIUS SCHULTZ, M.D.
Philadelphia, Pennsylvania

THIS paper is a preliminary presentation of a novel therapeutic approach to those conditions supposedly related to an excess liberation of histamine in the organism.

In 1936, Werle[7] reported the formation of a histamine-like substance when the amino acid, histidine, was incubated with rabbit kidney slices. Subsequent investigation[3,8] has confirmed the existence of an enzyme, histidine decarboxylase, which is present in animal tissues. In addition, it has been shown that bacteria of the colon-typhoid group possess a histidine decarboxylase which readily liberates histamine *in vitro* upon the addition of histidine.[1] Martin et al,[4] in an investigation of flavonoids, have demonstrated the total *in vitro* inhibition of histidine decarboxylase by d-catechin. An adequate explanation for this inhibition is at present lacking.

Further work by Martin and co-workers has shown that the histidine decarboxylase enzyme inhibition occurs *in vivo*. This conclusion was based on the protection against anaphylactic shock in guinea pigs offered by daily administration of d-catechin.[5] This seemed a fundamental approach to the therapy of conditions with possible histamine etiology.

In the present study a combination of d-catechin and the potent antihistaminic, dimethylaminopropylphenothiazine (Dimapp)[6] was used.* Dimapp (also known as Phenergan) has been shown to be fourteen times as powerful as the ordinary ethylenediamine antihistamines. The rationale of the therapy was to prevent the formation of histamine by inhibiting the histidine decarboxylase mechanism, and to pharmacologically counteract preformed histamine. The cases were selected from a routine medical practice and consisted of the following: frequent upper respiratory infection of allergenic etiology (eleven cases); bronchial asthma (six cases); urticaria (five cases); and sixteen cases variously diagnosed as contact dermatitis, Ménière's disease, persistent rash, severe penicillin reaction, grippe, headache and contact dermatitis due to an acrylic type of plastic denture.

At the outset, in general, doses based upon the dimethylaminopropylphenothiazine component were from 15 to 50 mg. Later it became evident that smaller doses ranging from 5 to 15 mg daily would bring about an adequate response in the majority of cases. The incidence of side reactions, in the form of drowsiness, at the higher level was 8 per cent (three cases); at the lower level, no drowisness was observed.

Results are presented in tabular form (Table I).

*Supplied by the National Drug Company of Philadelphia. Tablets contained 5 mg and 25 mg of Dimapp and 125 mg of d-catechin.

TABLE I. RESULTS

Patient	Age	Sex	Dosage*	Diagnosis	Clinical Results
1. M.M.	47	M	25 mg h.s. 3 mos.	Chronic upper respiratory infection. Healed T.B.	Patient believes incidence of colds lowered. No untoward reactions.
2. J.S.	37	M	5 mg t.i.d. 7 weeks	Frequent upper resp. inf.	Cold symptoms lessened. Slight tired feeling at times.
3. G.S.	26	F	25 mg h.s. 2 mos.	Frequent upper resp. inf.	Cold symptoms lessened.
4. I.P.	21	F	25 mg h.s. 3 mos.	Frequent upper resp. inf.	Cold symptoms lessened. If taken during day 25 mg causes drowsiness.
5. G.D.	32	M	25 mg h.s.	Frequent upper resp. inf.	Cold symptoms lessened. No side reactions.
6. H.G.	41	F	25 mg h.s. 3 mos.	Frequent upper resp. inf. from working in refrigerator room.	Taking tablets on first signs of cold for two nights would stop cold.
7. M.T.	54	M	25 mg h.s. 3 mos.	Frequent upper resp. inf.	Cold symptoms lessened. No side reactions.
8. H.Z.	34	M	25 mg h.s. 2 mos.	Frequent upper resp. inf.	Cold symptoms lessened. No side reactions.
9. G.I.	23	M	25 mg h.s. 8 wks.	Frequent upper resp. inf.	Cold symptoms lessened. No side effects.
10. G.I.	28	F	25 mg h.s. 11 wks.	Frequent upper resp. inf.	Cold symptoms lessened. No side effects.
11. S.D.	43	F	25 mg h.s. 8 wks.	Frequent upper resp. inf.	Cold symptoms lessened.
12. T.B.	42	M	30 mg/day 3 mos.	Chronic asthma.	Moderate relief; no side reactions.
13. E.P.	46	F	5 mg t.i.d. 25 mg h.s. 6 wks.	Chronic asthma since childhood.	Has received epinephrine injections 8-9 q.d. for 18 yrs. Only one injection necessary now.
14. D.P.	58	M	5 mg b.i.d. 25 mg h.s. 3 mos.	Asthma.	Bronchitis relieved.
15. M.T.	64	M	25 mg A.M. & P.M. 5 mg b.i.d.	Advanced asthma with mild cardiac decompensation.	Good results. No side reactions.
16. J.R.	56	F	25 mg h.s.	Chronic asthma and bronchiectasis.	No results. No side reactions.
17. C.W.	67	M	25 mg h.s. 5 mg t.i.d. 2 mos.	Chronic asthma, severe.	About 30% relief; 70% relief with intravenous aminophylline.
18. M.P.	48	F	30 mg/day 4 wks.	Urticaria.	No relief with epinephrine in oil. Slight relief at dosage level of 5 mg. At 25 mg urticaria all gone.
19. A.M.	55	F	5 mg b.i.d. 25 mg h.s. 3 mos.	Chronic urticaria.	25 mg h.s. helped, but calcium intravenously definitely stopped hives.
20. H.M.	37	F	5 mg b.i.d. increased to 25 mg b.i.d. 1 week.	Urticaria from penicillin.	Stopped rash in two days.
21. D.J.	49	F	25 mg h.s. 5 mg t.i.d. 1 wk.	Urticaria.	Good results. No side effects.
22. D.S.	42	M	5 mg t.i.d. 3 mos.	Physical allergy. Urticaria and frequent itching.	Stops urticaria. No side reactions.
23. M.C.	35	F	25 mg h.s. 5 mg 1 or 2 per day; 4 mos.	Severe frontal headache.	Sleeps better. Doesn't need Benzedrine during day.
24. M.H.	56	F	5 mg q.d. 25 mg h.s. 2 wks.	Occipital headache.	Stops headache if taken early.
25. M.S.	34	F	25 mg h.s.	Severe pre-menstrual headache.	Complete relief from headaches.
26. E.W.	50	M	25 mg h.s. 7 wks.	Allergic headaches.	Decrease in number and severity of headaches. No side effects.
27. F.R.	65	F	25 mg b.i.d. 3 wks.	Contact dermatitis of hands.	Helped a good deal. No side reactions.
28. M.C.	18	F	25 mg h.s. 1 dose.	Contact dermatitis.	No improvement. Drowsy following morning.
29. M.A.	60	F	5 mg t.i.d. 2 mos.	Persistent rash.	Marked improvement.
30. A.S.	46	F	25 mg h.s. 5 mg q.d. 2 wks.	Chronic dermatitis over entire body and extremities.	Rash is practically clear. No side reactions.
31. E.H.	43	F	25 mg b.i.d. 3 wks.	Mucosal irritation (allergy to dental plate).	Relief was marked. No drowsiness.

*Based on Dimapp.

TABLE I. RESULTS—CONTINUED

Patient	Age	Sex	Dosage*	Diagnosis	Clinical Results
32. A.L.	52	M	25 mg h.s. 5 mg b.i.d. 1 week.	Severe penicillin reaction.	No results. No side reactions.
33. A.S.	51	F	25 mg h.s. 5 mg t.i.d.	Severe penicillin reaction and serum reaction.	Slight improvement.
34. M.E.	24	F	25 mg h.s. 1 day.	Penicillin dermatitis, hives and grippe.	Stopped rash but was sleepy following day.
35. R.F.	56	F	25 mg h.s. 9 wks.	Allergic rhinitis.	Helps good deal. No side reactions.
36. M.K.	59	M	25 mg h.s. 8 wks.	Meniere's disease.	Number of attacks diminished. No side effects.
37. S.D.	39	M	5 mg t.i.d. 2 wks.	La grippe.	Cut symptoms. No side effects.
38. G.G.	24	M	5 mg t.i.d. 1 wk.	La grippe.	Symptoms lessened. No side reactions.

*Based on Dimapp.

RESULTS

The largest single grouping of cases fell into the category classified as frequently recurring upper respiratory infection. While our series is admittedly small, all patients reported relief of symptoms. Results in the asthma series were, on the whole, quite favorable. The most striking improvement occurred in Case 13, where the number of epinephrine injections was cut from an eighteen-year daily average of eight or nine to a single daily injection. On the other hand, there was no improvement in an asthmatic patient with concomitant bronchiectasis.

The five cases presenting urticaria responded quite rapidly except for one patient (Case 19) in whom it was necessary to resort to intravenous calcium before the urticaria could be controlled.

DISCUSSION

Feinberg[2] in his review of antihistaminic agents states that almost all of the methods proposed to combat the etiological effects of histamine are based on competitive attachment to the cell. In this series of cases the problem has been attacked in an entirely different manner, that of preventing histamine formation. At the same time, an effective antihistamine (Dimapp) was included to offset the action of preformed histamine. The therapeutic efficacy and low incidence of side effects seemed to reflect a synergistic action of the histidine decarboxylase inhibitor and the antihistamine. It should be noted that Shulman in his report on Dimapp states: "Dosages as low as 6.5 mg/day were frequently found sufficient."[6] In the three cases in our series with drowsiness as a side effect the dosage of the Dimapp was 25 mg. Further investigation will be undertaken at the apparently optimum level of 5 to 15 mg/day.

SUMMARY

Thirty-eight cases of frequent upper respiratory infection, asthma, urticaria, contact dermatitis, Ménière's disease, persistent rash, severe penicillin reaction, grippe, headache, and contact dermatitis due to an acrylic type

of plastic denture are reported. The therapeutic approach was by way of a combination of an antihistidine decarboxylase and an antihistamine. The results obtained were very favorable in the majority of cases.

REFERENCES

1. Best, C., and Taylor, N.: The Physiological Basis of Medical Practice. Ed. 4; p. 253. Baltimore: Williams and Wilkins, 1945.
2. Feinberg, S.: Histamine and antihistaminic agents. J.A.M.A., 132:702, 1946.
3. Holtz, P., and Heise, R.: Formation of histamine in the organism. Arch. f. Exper. Path. u. Pharmakol., 186:377, 1937.
4. Martin, G. J.; Graf, M.; Brendel, R., and Beiler, J. M.: Effect of vitamin P compounds on the action of histidine decarboxylase. Arch. Biochem., 21:177, 1949.
5. Martin, G. J.; Moss, J., and Beiler, J. M.: The inhibition of anaphylaxis in guinea pigs by d-catechin. (In press.)
6. Shulman, M.: Phenergan, preliminary report of chemical effectiveness. Ann. Allergy, 7:506, 1949.
7. Werle, E.: Formation of histamine from histidine by animal tissue. Biochem. Ztschr., 288:292, 1936.
8. Werle, E., and Herrmann, H.: über die Bildung von Histamin aus Histidin durch tierisches Gewebe. Biochem. Ztschr., 291:105, 1937.

2401 North 5th Street

ADRENOCORTICOTROPIC HORMONE (ACTH); ITS EFFECT IN ATOPIC DERMATITIS

(Continued from Page 10)

3. Randolph, T. G.: Allergy as a cause of nuchal myalgia and associated headache. Arch. Otolaryng., 50:745, 1949.
4. Randolph, T. G.: Cornstarch as an allergen. J. Am. Dietet. A., 24:841, 1948.
5. Randolph, T. G.: Differentiation and enumeration of eosinophils in the counting chamber with a glycol stain; a valuable technique in appraising ACTH dosage. J. Lab. & Clin. Med., 34:1696, 1949.
6. Randolph, T. G.: Fatigue and weakness of allergic origin; to be differentiated from "nervous fatigue" or neurasthenia. Ann. Allergy, 3:418, 1946.
7. Randolph, T. G.: House dust allergy. Arch. Otolaryng., (in press).
8. Randolph, T. G., and Rollins, J. P.: Adrenocorticotropic hormone (ACTH); its effect in bronchial asthma and ragweed hay fever. Ann. Allergy, 8:149, 1950.
9. Randolph, T. G., and Rollins, J. P.: Eosinophil observations in adrenocorticotropic hormone (ACTH) therapy. Proc. First Clin. ACTH Conference. Philadelphia: The Blakiston Co., 1950.
10. Randolph, T. G., and Rollins, J. P.: Relief of allergic diseases by ACTH therapy. Proc. First ACTH Conference. Philadelphia: The Blakiston Co., 1950.
11. Radolph, T. G., and Yeager, L. B.: Corn sugar as an allergen. Ann. Allergy, 7:651, 1949.
12. Rinkel, H. J.; Randolph, T. G., and Zeller, M.: Food Allergy. Springfield, Ill.: Charles C Thomas, (in press).
13. Rose, B.: Studies on the effect of ACTH on eosinophilia and bronchial asthma. Proc. First ACTH Conference. Philadelphia: The Blakiston Co., 1950.
14. Rowe, A. H.: Allergic toxemia and migraine due to food allergy. California & West. Med., 33:785, 1930.

700 N. Michigan Avenue

TECHNIQUE FOR SCREENING VERBATIM PSYCHOTHERAPEUTIC RECORDINGS AND ITS APPLICATION TO ALLERGY

HAROLD A. ABRAMSON, M.D., F.A.C.A.
New York, New York

THIS is a preliminary report on a research program in progress for several years.

The program at present consists essentially of two parts:

(a) Development of simple technics for the verbatim recording of psychotherapeutic interviews.

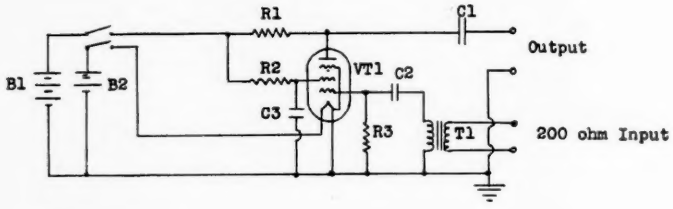
(b) Development of clinical and research procedures to make the voluminous data obtained by the verbatim recording of psychotherapeutic interviews applicable both to therapy and to the collection of basic material for the science of psychodynamics especially relevant to allergic patients.

Before recording is begun certain procedures are needed to establish proper rapport with the patient. The purposes of the recording are outlined to the patient in detail. Then several weeks are allowed to elapse before actual recording begins. Before recording is begun, anxieties which may develop in the patient toward both verbatim recording and the subsequent use of these recordings in research are noted. Recordings are begun only if the patient is desirous of having the data available for his therapy, for research, or both. The patient is informed that the data are his data; that the recorder may be stopped at any time; that nothing will be published without his approval; that through adequate editing identification by anyone other than the patient or doctor will be impossible. The microphone and recorder are out of sight of the patient but in the same room. In order to achieve a sufficient pick-up sensitivity it was necessary to use a preamplifier. The preamplifier was used with the Webster-Chicago Wire Recorder. At first the self-powered amplifier of General Electric Catalogue Number UPX-003 was placed in series with the microphone. This self-powered amplifier, however, produced too much superimposed hum. Finally, through the kindness of Mr. S. Ruttenberg of the Amperite Company, 561 Broadway, New York, N. Y., a battery-powered amplifier was provided and adopted (Fig. 1). This eliminated the superimposed hum entirely and increased the pick-up activity remarkably. The total cost of the recording and transcribing systems is less than $400. By using this battery-powered amplifier with the wire recorder, interviews are readily obtainable in which everything that the patient and physician say is readily recorded with good fidelity and can be transcribed easily.

Data were obtained in four cases of allergic eczema in female adults.

This investigation was supported by the Foundation for Research in Pulmonary Disease, New York City.

One might say that these patients represented a syndrome which is comparable to infantile eczema except that it persists into adult life. In all of these patients there was a most extreme disturbance in relationships with the parents. In three of the four cases the great hostility between



PARTS LIST

B1	67½ volt battery
B2	1½ volt battery
C1	.1 MFD 200 DCWV Cond.
C2	.005 MFD 200 DCWV Cond.
C3	.05 MFD 200 DCWV Cond.
R1	.47 Meg. ½ watt resis.
R2	1.0 Meg. ½ watt resis.
R3	10 Meg. ½ watt resis.
T1	200 ohm to grid transformer
VT1	Type 1S5 tube

Note – For High Impedance input, omit Transformer T1.

Fig. 1. Battery pre-amplifier made by Amperite Company, Inc., New York.

mother and child was an outstanding feature of this relationship. In the fourth case the over-solicitiousness of the mother was so binding upon the daughter that it masked an abnormal situation the nature of which could not be worked out without a psychiatric study of the mother.

The type of data obtained is best illustrated by what is believed to be a partial solution of the difficulty of handling the thousands of pages of single spaced typewritten transcriptions. The following useful *modus operandi* in psychotherapeutic recording of the type under discussion is given.

The patient was an allergic woman with a history of eczema, asthma and hay fever for many years. As the data of the recordings accumulated, it seemed desirable to develop a screening technique which would focus attention not on what was already known of and confirmatory of psychodynamic theory and technique but rather on what the patient herself had to say; for what the patient says comprises the basic data, the results of psychodynamic therapy. In this way, by excluding during the screening of the data what the therapist said and the dreams, what the patient said was readily collected to form the following basic and rather simple history categories or stories of the patient.

1. The relationship with the mother.
2. Relationship with the father.
3. Marital and sexual relationships.
4. Relationship with the children.
5. Relationship with siblings.
6. Relationship to work and to the community.
7. Clinical symptoms, signs and effects of drugs.
8. Relationship with therapist.

The typewritten parts of the transcribed recordings related to these stories are marked and then cut out of the typed copy. The categorized stories are pasted together in series corresponding to the number of the therapeutic interview. In this way the foregoing categories were developed and gave a direct and useful technique by which a life history of the patient's personal and work relationships were available for scrutiny as a continuous story. For example, the mother's story taken from the first fifteen interviews with one of these patients follows to show the possibilities inherent in screening material of this type.

MOTHER-DAUGHTER RELATIONSHIP IN ECZEMA-ASTHMA-HAY FEVER SYNDROME

A Screened Verbatim Report of the First Fifteen Interviews

First Interview.—One conclusion I came to, I think I started off with more of a maternal feeling toward John, my husband. That's why I think I am always looking out for him, in such ways, always have, always, from the very beginning. Another thing that concerns me a great deal is why, when I start off, why do I start thinking of my mother? Why do I start from way back there? Is it because I actually feel that there is some connection? Or, is it the place where I think I am supposed to begin, way back in my childhood? I blame a great deal on her also. I don't know if I blame it on her, or if I see a great deal. I know that there are a great many things that she did to me, that I am always trying to eliminate with my daughter Ann. I see myself doing that. And yet, I know she does those things and they bother me. She still persists, in certain ways, in certain manner of talking, in bossing me. Her domination still continues. Once in a while she will, I don't know if she realizes it, but she makes the remark she is not going to any more, and then I feel funny. I feel that I have pounced on her. I have made her feel that she has no right to intrude, although there are times when she shouldn't. She can't understand this at all.

She can't understand that there's no treatment. I have no salves, no lotions or anything to heal me up. I can't explain to her exactly what the process (of treatment) is. I don't think she would understand. She doesn't know when to stop asking questions, whereas John does. And, therefore, I can't go into it with her at all, because she goes so far. It is pretty hard to tell her, "I can't tell you that because I have no understanding of that either." I say to her, "I can't explain it to you. I can't tell you." I think I am at a difficult time right now because I actually am not living the usual routine of life that I usually have because I am running up to the hospital a great deal to take her place. And I have to do my work at home whenever I can, the fastest I can.

I think both my parents are pretty wonderful to be able to take care of themselves in this way, not actually depending upon my sister and me for anything at all, in the way of finances. My mother is working pretty hard right now to keep the business going, to go up and see my father, to go home and do the books at night, and to do things like that.

Third Interview.—I didn't do very much today because I haven't felt particularly well. I had another exasperating incident with my mother. I tried to start to explain to her a little bit, because she started asking questions again. She can't understand why I'm not getting more tests, or complicated lotions, or salves, or anything like that. She can't understand what I'm doing. So, I explained to her that you are taking a full case history so that you can really figure out what my allergy can be from. And she asked me if you are a psychiatrist, and I said well, yes, in a way and that you have studied psychiatry and everything. She wanted to know if I was erratic or something. I said, no, I didn't think I was erratic. She knows I have a lotion and that I'm practically on the way to recovery. It annoyed me, though, when she asked me if I was erratic, or not. Of course, I have to have someone staying with her, because she is rather tired and worn out these days, too. And I don't think she knows what she is saying sometimes. Of course, I'm leading up to the old situation again. I'm going to my mother's and staying there for a couple of weeks. I spoke to John about it last night and I'm glad he is honest with me, but he is not ready to go to live there again, even if it is only for two weeks. That goes back to the incident when he was there and I caught him with another woman. They had such a fight and he is still very embarrassed with them. I can understand, but, of course, it makes it difficult for me being there. I'm always very leery taking him up to my mother's house because I know he is not at ease, I'm not at ease, and I think that the whole air is tense. I'm always sorry that I have to go.

I remember another incident now; why I think of it, I don't know. The time when I lied about a Sunday School teacher, and it grew into a tremendous thing. This happened when I was thirteen years old. My sister had always won a great many prizes in Sunday School. I had always missed them by the skin of my teeth, and this one year I had worked very very hard. I got good marks, and there was one other girl in the class. The two of us were about even in marks. When the prizes were given out at the end of the year, she got the prizes. Of course, I was greatly disappointed and when I went home that Sunday, I think I told my mother something to the effect that the two of us were even and he let the minister decide who was going to get the prizes, or something like that. Well, that got back to the minister and he called up, and he wrote letters, and well, it ended up with an interview at the house. I tried to commit suicide the night before. I think I took eight aspirins. Yes, that was it. I was putting a white solution on my face and I kept looking at that and I kept thinking that there must be something in that that would poison me. Well, I didn't die and they came up to the house the next day, the minister and the Sunday School teacher. And I swore; I kept on; I didn't change my story; I still stuck to the story that he had said that. But it was such a, well, such a traumatic experience to me, that I swore to myself that no matter what happens to me, no matter what kind of beating I would get from my mother, no matter what, that I would not lie any more. I never did lie after that. Oh, I probably tell little white lies, but I never lied about other things after that. I tried as hard as possible to tell the truth, making no difference what it was at first. A friend of my mother's is involved in that. I don't know, there is a connection all the way through in many different ways. She worked there, in the church, and my mother told her the story, and

she went and told the minister, and that's how he learned the story. That's why I hated her at the time, too. I wasn't particularly popular. I wasn't very attractive when I was in my early teens. My father and mother knew I didn't have a lot of dates and this woman had two sons. My mother used to pester her as to why her sons didn't take me out. Of course, that embarrassed me a great deal. I didn't like her and I didn't like her sons because every once in a while they would ask me to go out and I would know why. And I remember that my mother forced them into inviting me to a party. It was the most miserable evening I have ever spent. That was the time I was having trouble with my feet again. And I couldn't wear my own shoes, so my mother made me put on her ugly, matronly shoes. I stood behind a piano all night so that nobody could see my feet. I felt—you can imagine how I felt, knowing that I hadn't been really invited to the party. My feet looked so ugly. They were bandaged. I had to wear white anklets underneath my stockings. I couldn't have any color next to my feet. That was a miserable evening. I hated them for that, and I hated my mother for that also.

I still don't know whether my mother believed them or believed me. I sort of think she must have believed me, because nothing was done afterwards. I mean, she didn't punish me. Nothing was said or anything like that. And usually when she caught me in a lie there was a great to-do about it? Therefore, I believe that she must have believed me, because it was finished with her after that interview. There are quite a number of bad experiences with my mother and with lying. There were a couple of times in school when I lied. I was in about the fifth grade, and I was probably around nine or ten years old. I think when I was seven years old there was a time, also, when I remember my mother had to come to school because of a bad mark on a paper. I wrote a note in her name that she was sick and couldn't come. The teacher realized that it wasn't in my mother's handwriting. There was quite a great to-do about that. The teacher sent a letter home and when I came home from school that day, my mother pulled me and cried and yelled, and screamed why I had done such a thing. I remember at that time I had a hard time learning how to spell her name. Until I had found out how to spell her name, I could not spell it. I was about seven years old.

I remember another time I used to keep a diary. This was about when I was fourteen. I told her I was meeting a friend of mine on a Sunday and when I came home I told her we had been to such and such a place. She didn't like it when I went to the movies too often. So, I told her I went some place else, probably a museum. I usually said a museum because that, she thought, was very good. I met my grandfather. I wrote all this in my diary and I hoped he wouldn't say anything to my mother. She took my diary once, and read it while I was there. Her reading it in front of me, and her finding out what I had done, was just terrific. I remember my sister was there also and she tried to stop my mother from doing it, but nothing ever stopped my mother from doing that sort of thing. We had very little privacy, as to diary, or mail, or anything like that. And my mother felt that anything that was ours was anything she could go into, something I resented very much, of course.

There was another time when I was tricky. When I was in high school—I was fourteen then, my first year in high school—the fleet came in and this friend of mine talked me into cutting school and going to see the ships. So, I got my mother to put her name on a piece of paper—any piece of paper—and told her that we were tracing heredity by tracings of handwritings, or something like that, in biology. She did it. And then I wrote a note over her name which excused me from school, and we went down. Very stupidly, I kept the note that I had written in my notebook and she found it. Well, she called me all sorts of things after that. We just saw the battleships and came home, that was all. There was no picking up

of sailors, or anything like that. We just wanted to see the ships. My mother's one feeling was that we should keep away from those battleships, and those sailors who rape you, and all that kind of stuff. So, of course, when she found out what I had done, she called me all sorts of names, that I was a bum, a tramp. She spit in my face, and I thought I was a bum, a tramp too, the way she went about it. That was another big scene in my life.

I've never been close to my mother. I couldn't tell her what I really think, or what I feel about something. I think I fool her and myself. I talk one way to her, but I feel differently about it. But I'll say it because it would make her happy. Right now with my treatment, I just can't see why I can't say "I like the treatment and don't ask me questions." Well, I did say it last night because she made me angry by asking me if I was erratic, or not. I said to her that if she was going to ask me questions I was going for two or three years. She stopped and ended up saying, "You're satisfied, aren't you?" and I said, "Yes." She doesn't mean it when she says that. She still has the feeling that I am a little girl who has to be taken to the doctor by the hand, and she will sit and do the talking. She usually likes to direct the doctor. My sister is very helpful and understanding at this time. I don't like to tell John all these things, these feelings I have toward my mother, because I think he has enough hostile feelings toward her all by himself and I don't like to add to them. So, very fortunately, I am able to tell my sister. She says to me, "You go ahead and tell me what you want; after all, I can understand." I can say a good many things. She probably treats my sister the same way that she treats me. My sister accepts it in such a different way! Sometimes I think she should *mix* more than I do right now, and at other times, I think she flares up much more. I usually don't have as many arguments, or as many flareups as she does, because I have sort of formed the habit of saying yes, and doing as I please because I find that is easier than having an argument.

Fourth Interview.—My mother is still concerned whether I'm getting good treatment and proper treatment. I just realized yesterday that if she doesn't know the doctor I'm going to, she isn't in accord with it before I even begin. She is not quite sure that I'm going to a good doctor. And, it happened when I was down in Boston because it was there she kept nagging me about going to a good doctor. How do I know he's good? Her idea then was that there were no good doctors in Boston. There are only good doctors in New York. It is the only place where good doctors congregate. She still has the same feeling. And I told her point blank yesterday that I couldn't stand the questioning. Her idea is that unless she shows interest by asking questions, she is not concerned about me. I told her I will be much happier if she is not concerned about me, and if she'll leave me alone, I'll get along much better. I spoke to my sister about this and I told her how my mother bothered me. She was along with me yesterday when I saw my mother in the hospital.

I have no desire for her to come to see you, as I have no desire for you to be bothered by her. I feel that in time she will get to realize that, with my constant repetition and my constant answering. I didn't get excited, or anything. We joked and laughed about it in a pleasant way, and I feel in time she will begin to realize that I'll feel much better. It struck me so funny yesterday because she said to me, "He gave you a lotion, now, didn't he?" And I told her I had a lotion, but I didn't tell her what the lotion was. I didn't tell her that it was just calamine and phenol because that would disillusion her greatly. So, she is very happy that I have a lotion. As I said before, she is only interested in the superficial cure. I know I'm going to improve, so that if I bide my time and when she sees improvement she will be satisfied in time also. But I have no desire for you to be bothered by her.

It hasn't entered my mind that I even want you to talk to her. It never entered my mind.

Fifth Interview.—I started thinking the night before last. John didn't come home till late and when I went to bed I started thinking a little bit. I was wondering what was upsetting me. I was scratching and I itched. And I started thinking that maybe moving back to the city when my father comes home has me disturbed at this time. What exactly about it disturbs me, I don't know. Whether it is because John isn't in accord with the idea, or because of what will be said when my mother finds out that he doesn't want to stay at the house (and I know that there will be a great deal of discussion) and when I say discussion I mean that it will be reassuring her that we should go home. I would not be able to say to her that he doesn't want to sleep there because he is not comfortable. I wouldn't be able to say that to her. And I'd have to have mighty good reasons to give her. I'm pretty sure it's the idea of telling my mother and giving her reasons why John wouldn't be staying at the house, because she expects him to, right now. I think these are explanations of the tension between John and my mother. I didn't realize it, though, except at this time I'm thinking about it a great deal, more than I usually do.

I wanted to ask you whether I should, or not, stay at my mother's for a couple of weeks. I know you are asking me not to change things too much in my life right now. There won't be anyone to take care of my father, unless we get a practical nurse to come in and take care of him, because my mother is taking care of the business right now so she isn't home all day. And, of course, he isn't able to take care of himself just yet, and he won't when he comes home. That was one of the questions I wanted to ask you whether I should, or not. Of course, I ask myself the question if I have to go out and buy a bed it is just as worth while for them to hire a practical nurse. Well, not the same amount, but still they're spending money anyway. But then I imagine my mother would feel still better and more comfortable and perhaps my father also would, if it was someone he was close to. After all, a strange person coming into the house, she doesn't know anything about where things are in the house, and nobody would be there to show her; therefore, it would be easier for them if I came in and stayed there. I'm sure my sister would come in a few days to relieve me. But they have to be sure of someone being there at all times, and it's easier for me to sleep there also than to run in early every day and every morning from home. And if I'm going to take care of them, I would rather sleep there than travel back and forth every day. So I don't know when I started thinking about it and when I end up.

It's not that I come to the conclusion that the only thing I can do is to go. I sort of want to. I was disturbed that he had another woman. I never visualized him with another woman. It was just what he was doing to me, not what he did with another woman. At that time I didn't even worry so much. I didn't think about it. My mother used to question me and the first couple of times I didn't realize it, but after a while I did. I asked him where he had a meeting, whom he had a meeting with and things like that, to find out if I really knew where he was going and what he was doing. At that time I wasn't suspicious of him. I didn't worry about it. My mother is funny. She used to drill into us—such as what do we do when we get up in the morning. Do we dress nicely? Do we comb our hair? "Maybe you ought to put a little lipstick on." It was her asking every once in a while if I still took care of myself. Her point is this. He's so good looking that women fall over him, and I have to make sure I keep myself nice looking. I like to keep myself nice looking and clean looking, but to such a point that it became

ridiculous to me after a while. Her worrying about it like that. And it was silly to me that all the women—and he does meet a great many because of the organizational work that he does—that they all fall all over him and swoon over him. Most of them are much older than he, and I can't see what influence they will have over him. He has so many opportunities to meet much younger women than those. Flattery does mean a great deal to him, and he likes to be flattered just as much as anyone else. It's when I start thinking about it, a great many things my mother has put in front of me that I wouldn't see myself. And that is another question I debate inside of me a great deal. Would I be better if I didn't see a great many of these things? Or should I see them? They are inconsequential, actually. I'm living with the person and if they don't bother me, to begin with, why should the thought be put in my mind? I don't like it at all.

Sixth Interview.—I awoke one morning and couldn't see. That was when I had keratitis. I drove into the city with him (husband) then. It was a year ago, last spring, and he dropped me off about a half a block away from the doctor's. He let me walk in by myself. I almost fainted on the street because I was so bewildered and couldn't see. Then when I called him up and told him I had to go to the hospital and asked him to take me down, he didn't know whether or not he could make it because he had an appointment. And so I had to go running around to find my mother to see if she would take me to the hospital. Going home it was the same thing.

So, when I left the hospital I felt sick myself. There still was no John to call upon. I still had to call my mother up to get me, but he happened to come back about two minutes before my mother came and so he drove me home. We argued about my being with my mother a great deal and yet he forced me to call upon her. And then when I did call upon her, he resented it. He didn't like it at all that I went home to her house afterwards.

Seventh Interview.—What bothers me more is my mother's strain, the business and getting rid of it. And the sort of, I think, the lackadaisical attitude on my part also, in letting things ride, such as the fact that he should have gotten rid of the business last winter when the heart specialist told him to, and he said so again. Nothing was ever done about it. Of course, it is rather difficult for me to interfere with their affairs. They keep things, those kind of things, they have always kept to themselves. That is, they never consulted my sisters or me, or brought us into any of those matters. I feel that if we would have pushed them a little bit, they would have done something about it. That would have made things much easier than they are. And yet, my mother still can't make up her mind to get rid of the business. Some will tell her "Yes," and some will tell her "No." She just can't make up her mind. The funny part of it is that I sometimes think she should keep it, and other times I feel that she should get rid of it.

Eighth Interview.—When I first started studying law, that is, when I first started in college, or when I first started discussing what I was going to study when I went to college, that was the one thing my mother had always built into me so very much, that I had security from the fact that I had my license to be a lawyer. She had two friends, and their husbands took sick, and they were able to go back to support the family by being educated. I think that feeling is still in me even though I don't realize it.

I think maybe I'm reluctant to talk also because I found my mother saying so often over and over the same story. I get tired of it. I find it more trying to be

with her right now, than even the worry over my father. I find it more difficult to stay with her, doing things that she does, saying things that annoy me. She thinks, she realizes that, well, sometimes it just seems so dramatic to me and I can't stand it. I can't see it. Maybe she's expressing herself as she feels, to every single person that she sees and talks to. And then there are things, too, that are annoying. Maybe it is again one of my faults, of keeping my feelings to myself and not really expressing how I feel. But, then, I think again that there are things I just can't express, no matter how I want to, and I just leave them unsaid. Maybe because my father hasn't been, well, much of a dominant or influential person to me. My mother was so dominating. She dominated him, us. It was her words always that you went by. Yes, when we were younger, we had to please my father, but he was held up as someone away from us. Of course, she has always sort of been the leader for him. That is, she egged him on to different business deals and doing different things, financially. Other things she wouldn't even consult him about—just go ahead and do it herself, and he always let her. I sort of resent now, too, when she is so concerned about him. It seems to me that she knew, that she has been told also that his condition was so bad. I suppose she didn't do much about it. She would aggravate him, which did him no good either. And, oh, he told me once that she even started imitating his burping, which is really only from nervousness most of the time. She'd keep him out late. She'd always keep saying to him, "Well, go home by yourself," and, "Get up and leave." He would never go against her. I think he was always afraid of an argument with her. I think he tried, he tried to do everything possible so that there wouldn't be an argument, because of my mother's violent temper. A great many people like my father, all sorts of people really feel concerned about him. (I always felt as if my mother was always the one who overshadowed him so that people just didn't see him, or something like that, and yet it's not so.) I found out they are concerned about my father, about him, and not because he's married to my mother.

Ninth Interview.—I've been thinking about something these last couple of days. I don't know if I told you that day, I was with my mother. My husband goes home and I see him for a while in the evening. He goes home afterwards. These last few days I was filled up (asthma) considerably. Now I take no sedative at night and I sleep very well, thank goodness. These last couple of nights I have only awakened once each night and I've scratched very little, and it puzzled me a great deal. I was wondering if I changed my environment, so to speak, and it had the effect upon me that I feel like this. I take no sedatives, or anything like that. I itch less than I used to. I was wondering what's going to happen when I go home again and I start in with the same old routine.

Tenth Interview.—Well, our argument started over nothing. My husband wanted to know what we had in the bank. I was making out checks. He wanted to know what we had left in the bank and I told him. He then grabbed the check book. I had papers in it and I grabbed at the same time, so that the papers wouldn't drop out. Well, he became very annoyed because he thought that I was trying to keep him from knowing what we had in the bank. I found out this morning the reason why he became annoyed. He thought I was doing the same thing that my mother had done to my father. She didn't tell him what was in the bank. But my father never concerned himself about it and so if he would have asked, my mother would have told him. I don't know how things went, or where he got the idea that my father never knew what they had. I don't know, but this morning he remarked to me that I wasn't going to do to him what my mother had done to my father, and that is to keep him from what he had.

Eleventh Interview.—One nipple on my breast is very sore. I find that wearing a pajama top is too warm around my neck so I have been wearing a brassiere. First I put a layer of vaseline, or ointment on and then after I put a piece of cotton, or a piece of gauze, over that on the nipple of my breast. After that I put the brassiere on.

Well, the first thing that I would say is that my mother would always usually check up medications. First of all, it is very important to her to feel that that's going to heal me; secondly, I say that she still has that feeling that she must see that I put on my medication, that I take my medicines. My mother also had a rash on her breast and she told me what she did. I was even doing this before my mother. She told me that she put boric acid ointment on also and that it healed her up. She's funny. Well, every day she will remark that I look better. I know that in the last couple of days she doesn't mean that I look better than I did before, because I don't. I think that inside of her she would like it if I did heal up because I am living at her home right now. She said it last night in front of my husband. I think I told you before that he and I discussed the fact, and he feels very funny that I was sleeping at my mother's and I healed up at that time. And she said it last night in front of him. He said "Well, she's just teasing me," because we joked about it then, but I think she got some sort of satisfaction out of it.

That's another thing, the other night, my mother, my husband and I were together, and at that time I started scratching. He saw that I had opened my skin and I was bleeding. It was around my eye and he gets very angry when I do those things, and my mother burst out, aggravated, "Can't you make her stop doing that?" or something like that. Usually, I can ignore it, but I guess because the two of them jumped on me at the same time I became rather annoyed.

Twelfth Interview.—I feel that I am the sole judge as to whether I am satisfied or not, with the medical treatment that I am getting. I had to convince my mother at great length, that I was satisfied, that I was the one going to the doctor, and that I was the one to decide whether I was getting the proper medical attention or not.

Thirteenth Interview.—I would say up until the time that I met John, I kept everything within myself. I had no one to go to and talk to. Then when I met John I think I told him a little of my feelings. I think he was the first one I ever told about my feeling of insecurity. I was graduating from college at that time, and I was very much afraid that I might not get a job, and he was the first one I ever told anything like that to. I told him a few things like that, but most of the things I kept to myself. I never have really been able to express myself. Usually, I keep things within myself. I used to say I took after my father like that. I feel that my father does the same thing. I feel that he has kept a good many things inside himself for, well, up to about a year or so, when he started talking to my sister and me. I often identified myself with my father and with my father's family. When I was lying, my mother always used to tell me that I was like an uncle of mine, on my father's side, whom she called a chronic liar, one who couldn't tell the truth, who always lied. It ever frightened me sometimes to think that surely I was going to be a chronic liar like my mother called me. I was pretty proud of myself when I stopped lying because I felt that it took a great deal of effort and that I had really accomplished something. I had really gotten myself out of this horrible habit that was so awful.

Well, the first lie that I remember was when I was in public school, when I was about six years old. I should say that was the first lie they caught me in, that I remember, and that was when I lied to the teacher and told her that I had a baby

brother. She knew that I didn't because she had just seen my mother the week before and my mother didn't look pregnant. She called my sister down to make sure that it wasn't so and I started crying when my sister came. I remember the teacher took me on her lap and she didn't ask me why I had said I had a baby brother. She asked me why I had lied. And I just kept saying, "I don't know. I don't know." When people said I looked like my mother, I used to fight, really fight, that I looked like my father. A great many people tell me I talk like my mother, that is, our voices are alike when we speak over the telephone. I don't get much satisfaction out of it. It's funny sometimes, though, just like a joke, when people get fooled or something like that. Otherwise, I never really enjoyed it. Yes, I'm annoyed now when he (husband) lies, because as I said, I felt that I had accomplished something when I stopped lying. I found that it wasn't necessary to lie, that one can live without it. I found that if I had done something wrong, instead of lying about it, it is just as easy to tell the truth and that's the way I feel with him. Also, I had great fear of my mother. I had great fear of being hit, of being caught in a lie.

Fourteenth Interview.—I didn't take the sedative at all when I was at my mother's. I didn't even have it there either. I didn't need it. Yes, I occupied the same bed when I was sleeping with my mother.

Well, as I said, I don't think I had any body contact with her. I never woke up, but I was never touching her.

Fifteenth Interview.—Toilets also remind me of my mother drilling into me never to sit down on a public toilet because of the diseases I'd catch, and I even asked her, "If I put paper down?" "No, that isn't enough. Just never sit down on a public toilet." When I was taught about the diseases that you can catch from a toilet seat, I didn't know what exactly the diseases were; but I knew that they were something horrible, something to be feared very greatly. That was one thing about my mother. She instilled great fears into you without really explaining them and you believed them. Yes, I believed them and obeyed them, not only from the fear that I might get a disease, but if I did get it she would find out that I had not obeyed her.

DISCUSSION

Mitchell and his co-workers as well as others have published recordings of verbatim interviews on allergic patients.[4] The technique was non-directive. The present report and screening technique is adapted for more directed therapy in which unconscious material is utilized by both patient and physician.

A further development in the therapeutic procedure has been that in which the patient reads a selected part of his own verbatim story relating to specific problems and is asked to comment on the story and discuss his own progress. The patient's remarks on his own data are also recorded. These data will be subsequently reported in detail in collaboration with Dr. J. A. P. Millet.

Although verbatim recordings result in an unusually large volume of transcribed psychological material, using the technique described in the foregoing, it is believed that the records will provide a rich source of data readily accessible to psychodynamic investigation and interpretation for

the formulation of psychodynamic theory. It will also serve as an aid to the therapist in treating the patient.

The construction of any science requires that the same facts be collected, assembled, and made available for study by independent observers or that an experiment be reproducible. The science of psychodynamics, although dealing with unmeasurable quantities, is believed to be amenable to the same basic operational procedures of any science insofar as collection of data is concerned. It is believed that the screening method herein outlined provides a vital part of a general procedure, the whole of which, with the additional study of the remainder (dreams, et cetera) of the record in relationship to what the patient says and does, will provide a necessary base for the future of psychodynamics as a science. Just as in a physical experiment, the large number of physical events occurring simultaneously must be isolated, collected, and screened for physical interpretation, so do the verbatim recordings of psychological events make themselves available for isolation, collection, and screening for psychological interpretation.

I should like to make a preliminary statement on what appears to be a result of importance to the practicing allergist. This is the nature of the threatening relationship of the mother (parent) to the child who retains, for all practical purposes, infantile eczema in adult life. This eczema, together with a threatening relationship, begins at an early age when the prototypes of later guilt feelings are developing in the child. This fear of the psychologically threatening mother who does not recognize the true situation is not therefore so complicated by unconscious guilt of more mature type (Miller and Baruch).[2] The reaction of the child and adult is characterized by a simple and violent infantile reaction to the threatening parent by a retaliatory attack on the only object the infant can attack—itself. It is thus that the allergic adult with persistent infantile type of eczema meets certain threatening daily life situations; their threatening nature is matched by a persistent and infantile form of retaliation—scratching in areas already prepared by an allergic constitution.

REFERENCES

1. Miller, Hyman, and Baruch, Dorothy W.: Emotional traumata preceding the the onset of allergic symptoms in a group of children. Ann. Allergy, 8:100 (Jan.-Feb.) 1950.
2. Miller, Hyman, and Baruch, Dorothy W.: Maternal Rejection in Allergic Children. (Presented before the Fifth Annual Convention of The American College of Allergists, Chicago, April, 1949.)
3. Miller, Hyman, and Baruch, Dorothy W.: Psychosomatic studies of children with allergic manifestations. Psychosom. Med., 10:275, 1948.
4. Mitchell, John H., and Curran, C. A.: A method of approach to psychosomatic problems in allergy. West Virginia M. J., 42:1, 1946. See also Mitchell, J. H., In Harold A. Abramson: Psychodynamics and the Allergic Patient. St. Paul: Bruce Publishing Co., 1948, p. 68.

TREATMENT OF BRONCHIAL ASTHMA WITH PREGNENOLONE ACETATE

A. OLIVEIRA LIMA, M.D., F.A.C.A.
Rio de Janeiro, Brazil

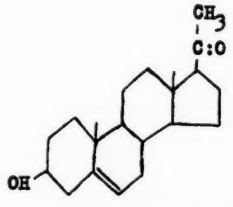
THE beneficial effects of cortisone in various diseases in which allergic inflammation has been considered of primary importance, suggested the possible application of other hormonal steroids in these conditions. Pregnenolone has been focused upon because of (a) its possible role as a precursor[6,8,11,12,13] of more active steroid hormones; (b) its lack of toxicity; (c) its efficacy when administered orally (d) its relatively low cost.

The experimental studies of Seifter et al,[10] showing that 21-acetoxypregnenolone is as effective as cortisone upon the permeability of rabbit synovial membranes and that this substance antagonizes the effect of DOCA and hyaluronidase on these membranes, and the favorable clinical results obtained with pregneninolone in rheumatoid arthritis,[2,3,4,5,7,10,14] suggest the trial of this substance in other allergic conditions.

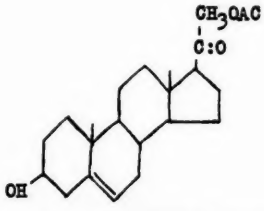
PREGNENOLONE

Pregnenolone was prepared chemically by Butenandt in 1934 and was obtained by extraction from hog testes by Ruzicka in 1943.

Pregnenolone (Δ^5-pregne-3β-ol-one) is compared structurally with progesterone. It should not be confused with pregneninolone (Δ^4-pregne-20:21-ine-17β-ol-one), known clinically as anhydrohydroxyprogesterone. Pregnenolone, like many other steroid substances, is usually prepared in the form of acetate.



Δ^5- pregnenolone



21 - acetoxypregnenolone

Pregnenolone has an adrenocortical activity,[12] described as similar to that of desoxycorticosterone, but of lower intensity. It improves fatigue apparently by sparing[9] adrenocortical activity. It is believed that pregnenolone operates in the body by being first converted into some more familiar steroid hormones.[6,8,12,13]

The substance has an extraordinarily low order of toxicity. Daily

From the Department of Dermatology, Medical School, Brazil University, Rio de Janeiro, Brazil.
Pregnenolone, Fontoura Wyeth, S.A., Brazil.

TABLE I. SOME CLINICAL AND LABORATORY DATA OF THE TWENTY PATIENTS

Data	Patients																			
	A.L.	J.M.L.	S.T.R.	N.V.	B.A.	A.S.	D.C.	O.F.	M.C.	J.R.T.	A.M.	C.S.M.	J.S.	N.M.L.	N.G.	C.F.A.	F.M.	N.S.	P.M.S.	S.P.
Age (years)	20	23	38	40	27	31	32	33	40	38	37	30	31	33	30	30	35	31	40	40
Sex	M	M	F	F	F	F	F	F	M	M	M	F	F	M	F	M	F	M	F	F
Beginning of the First Symptoms (years)	3	8	13	12	10	20	9	8	6	13	12	10	10	12	7	4	3	5	6	12
Type of Asthma	P-S	P-S	P-S	P-M	P-M	P-M	P-S	P-S	P-S	P-M	P-M	P-S	P-S	P-S	P-M	P-M	P-M	P-M	P-S	P-S
Other Symptoms	PR N	PR	PR	PR	PR N	PR U	PR U	U	U	PR	PR	PR	N	PR	N	N	PR	PR	PR	PR
Allergens Discovered	HD K M	HD K L	HD F	HD M W	HD L M	HD L W	HD W F	HD W L	HD W M	HD F	HD L	HD L W	HD F	HD L K	HD K F	HD K M	HD M L	HD K W	HD W L	HD F
Vital Capacity	2.000	1.800	1.700	1.200	1.900	1.500	1.600	2.100	1.800	1.000	1.100	1.300	1.400	1.200	1.800	1.700	1.800	1.800	2.100	2.000
Sedimentation Rate (Wintrobe)	12	18	15	14	7	18	20	19	16	14	20	21	30	15	12	10	12	15	14	10
Total Blood Leucocytes (cmm)	6.000	9.000	6.500	7.000	8.500	6.500	6.800	8.000	9.000	7.800	6.500	6.000	7.100	8.000	7.000	6.800	6.000	7.000	7.500	7.800
Blood Eosinophils (%)	4	8	10	12	15	18	17	12	10	8	7	9	11	13	10	10	8	9	12	15
Blood Lymphocytes (%)	25	30	31	30	25	20	21	23	28	31	29	25	20	25	30	29	30	32	40	38

P—perennial; S—severe; M—moderate.
PR—perennial rhinitis; N—neurodermatitis; U—urticaria.
HD—house dust; K—kapok; M—molds; W—wool; L—linter; F—foods.

doses as large as 600 mg can be employed without danger of deleterious effects. The compound is stable, either in dry form or in solution in propylene glycol or sesame oil.

SUBJECTS AND METHOD

Twenty patients with chronic bronchial asthma were selected for this study, including twelve women and eight men, with ages ranging from twenty to forty years. The duration of the disease varied from six to fifteen years.

The patients, as shown by x-ray and clinical examination, had no evidence of pulmonary or cardiac pathology. All patients were treated by the usual allergic methods without satisfactory improvement. In table I are condensed the principal clinical and laboratory data concerning these patients.

Each patient was given daily 400 mg of pregnenolone acetate, by two intramuscular injections of 200 mg each, for fourteen days. The preparation was given without the patient's knowledge of the nature of the material. Dietary or other environmental changes were not made during or immediately after this treatment.

In addition to studies directed toward an evaluation of asthma, the patients were observed for evidence of any untoward reaction to pregnenolone acetate. Frequent determinations of vital capacity, blood pressure, total and differential leukocyte blood counts, sedimentation rates, and urinalysis for glycosuria, were made during and after the treatment.

SUMMARY AND CONCLUSIONS

1. Pregnenolone acetate in a dosage of 400 mg, administered intramuscularly over a period of fifteen days, was ineffective in the treatment of twenty patients with allergic bronchial asthma.

2. It had no effect upon the blood pressure, sedimentation rate, total blood leukocytes, and relative percentage of lymphocytes and eosinophils, during or immediately after the treatment.

3. It did not change the skin reactivity of the individuals to food and inhalant allergens.

4. It did not increase the effectiveness of epinephrine and aminophylline in relieving asthmatic symptoms.

5. No deleterious effects from pregnenolone acetate were observed, nor any unpleasant side effects.

REFERENCES

1. Bruzzone, S., and Lopez, H.: Comparative cortical action of different pregnenolones in the adrenalectomized guinea pig. Proc. Soc. Exper. Biol. & Med., 68:579, 1948.
2. Davis, J. S., Jr.: Cited by Henderson.[5]
3. Davison, R.; Koets, P.; Snow, W. G.; and Gabrielson, G.: Effects of delta 5 pregnenolone in rheumatoid arthritis. Arch. Int. Med., 85:365, 1950.

(Continued on Page 44)

SOME PHARMACOLOGICAL PROPERTIES OF 2-[PHENYLBENZYL-AMINOMETHYL]-IMIDAZOLINE HYDROCHLORIDE (ANTISTINE), AN ANTIHISTAMINE

B. N. CRAVER, M.D., Ph.D., W. BARRETT, A. CAMERON, E. HERROLD, and F. F. YONKMAN, M.D., Ph.D.

Summit, New Jersey

SINCE all of the methods employed in this study have been previously described in detail, needless repetition has been avoided by giving the appropriate reference after each preparation.

Isolated Tissues.[1]—The potency of the drug in antagonizing histamine-induced and acetylcholine-induced contractions of the isolated ileum of the guinea pig was determined. Its actions upon the spontaneous activity of the isolated feline uterus and of the isolated duodenum of the guinea pig were also investigated.

Bronchioles.[15]—The action of the drug in antagonizing histamine-induced bronchiolar constriction in the perfused lungs of guinea pigs was investigated. Guinea pigs were also exposed to an aerosol of histamine until convulsions developed. Subsequently the doses of the drug were determined which, when administered intraperitoneally twenty minutes prior to the exposure, would prevent the development of convulsions during another exposure for the standard interval of three minutes. The apparatus employed has been described.[13] The air pressure was adjusted so that control animals convulsed in less than two minutes. Treated animals that failed to convulse within three minutes were removed at the end of that interval and thereafter re-exposed hourly for the same period, until such time as they convulsed during the exposure.

Anaphylaxis.[4]—Male guinea pigs were sensitized by the intrahepatic injection of horse serum, and after three weeks the doses were determined which would protect the animals from death when given intraperitoneally thirty minutes prior to the injection of a shocking dose of horse serum administered via the penile vein. This route of administration eliminates the risk of cardiac injury with its possible sequel of hemopericardium, which can lead to a confusing train of symptoms difficult to distinguish from those of anaphylactic shock. In this experiment the protective action of Pyribenzamine served as a control. Two doses of each drug were administered intraperitoneally: one-half and one-third their respective intravenous LD_{50}'s in white rats. This was thought to give a more valid basis for comparison than injecting identical doses by weight of two drugs

Antistine was prepared by Miescher, Urech and Klarer,[14] and the results of its initial pharmacological investigation were reported by Meier and Bucher.[14] The present paper presents results confirming and extending their studies.

From the Research Department, Division of Macrobiology, Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

differing so much in toxicity. Neither dose of either drug caused symptoms in the guinea pigs.

Feline Salivation and Nictitating Membrane.[17,19] The effects of the drug upon salivation induced in the cat by intracarotidly injected histamine dihydrochloride, as well as upon the contractions of the nictitating membrane simultaneously induced were investigated.

Thiry-Vella Dogs.[8]—A brief, duplicable intestinal contraction was induced by the intravenous injection of suitable doses of histamine dihydrochloride into anesthetized dogs fitted with Thiry-Vella loops. The doses of the drug were determined which when administered prior to the injection of the "control" dose of histamine would just prevent any intestinal response.

Histamine-Induced Hypotension.—The procedure described by Wells and his associates[16] was employed for assaying the activity of Antistine in antagonizing the hypotension induced by varying doses of intravenously administered histamine diphosphate.

Isolated Hearts.[2]—The effects of the drugs upon the isolated, perfused hearts of several species were determined.

Cerebrospinal Fluid Pressure.[7]—The effects of the drug upon the kymographically recorded cerebrospinal fluid pressure of the cat and of the dog were investigated, as well as its activity in preventing the changes induced therein by intravenously injected histamine.

Anesthetic Action.—The procedures and results of this study have already been separately reported.[18]

Cilia.[8]—This method involves the use of a frog's esophagus with carmine particles as an "indicator" of ciliary activity. The effects were observed directly by the use of a binocular dissecting microscope.

RESULTS

Isolated Tissues.—A concentration of 0.2γ/ml Antistine hydrochloride was found to inhibit by at least 95 per cent a subsequent response of an isolated ileal strip from the guinea pig to 1γ/ml of histamine diphosphate. This was the lowest dose found effective. With some strips of gut 1γ/ml was found necessary. Antistine exhibited one peculiar effect that we have not previously encountered with antihistamines: a lower dose of Antistine would suffice for the first "test" to eliminate the response to histamine than might be found necessary in subsequent repetitions of the "test." A "test," represented by Figure 1, comprises the establishment of duplicable responses to a control dose of histamine, the addition of the antihistamine, the elimina-

tion of the first response to histamine given two minutes after the antihistamine, and, finally, restoration of the control responses to histamine after the antihistamine has been washed from the bath. It was found

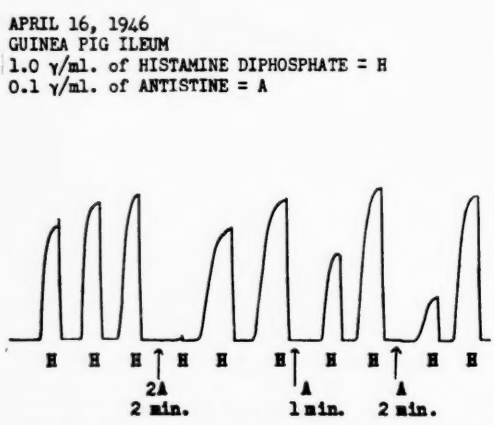


Fig. 1. 0.2γ/ml of Antistine eliminated at least 95 per cent of the spasmogenic action of 1γ/ml of histamine diphosphate added to the bath two minutes after the Antistine. One-half that dose was insufficient to eliminate the response to histamine. It may be observed that one minute of waiting after the addition of the antihistamine before adding histamine was too short an interval for the full action of the antihistamine to be asserted. The tissue was washed after each addition of histamine.

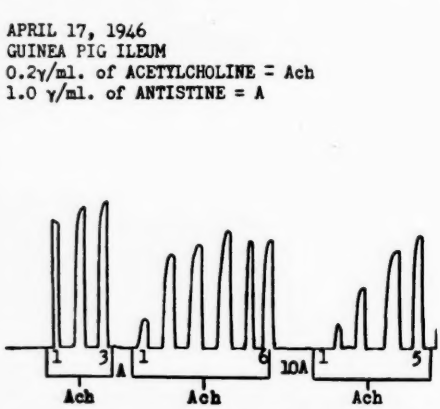


Fig. 2. 1γ/ml of Antistine significantly inhibited the response to 0.2γ/ml of acetylcholine hydrobromide added to the bath two minutes after the antihistamine. Ten times that dose of Antistine, however, was required to eliminate the response to acetylcholine. The tissue was washed after each addition of acetylcholine.

that 10γ/ml of the drug was required to inhibit by at least 95 per cent the response of the same tissue to 0.2γ/ml of acetylcholine hydrobromide. These results have been illustrated in Figure 2. It may be observed that

TABLE I. PROTECTIVE ACTION OF ANTISTINE FOR GUINEA PIGS EXPOSED TO FOG OF HISTAMINE

Dose Mg/Kg	Cumulative Number of Pigs that Convulsed by End of Indicated Interval in Hours								
	0.5	1.5	2.5	3.5	4.5	5.5	6.5	7.5	8.5
3.9	4	8	10	11	13	13	14		
7.8	0	1	5	6	7	9	12	12	14

Conditions: Exposure interval of 3 minutes to a fog of 0.02% histamine dihydrochloride produced by an air pressure of 6 pounds.
6 controls exposed to this fog convulsed in from 51 seconds to 97 seconds.
15 animals for each dose level.

the full inhibitory effect of the antihistamine was not exerted unless at least two minutes had been allowed to elapse after the addition of the drug. Shorter intervals would tend to emphasize undue differences in the rate of absorption by the tissue of an antihistamine. The isolated uterus of the guinea pig proved about as sensitive to the stimulating action of Antistine hydrochloride as it is to the action of Pyribenzamine hydrochloride. Little or no stimulation was caused by 1γ/ml but 10γ/ml caused appreciable stimulation. The uterus of the cat *in vivo*, however, responds relatively poorly to intravenously injected antihistamines.

Similarly, 10γ/ml had little effect upon the isolated duodenum of the guinea pig, but 100γ/ml appreciably inhibited its activity.

Bronchioles.—With perfused guinea pigs' lungs, concentrations of from 1 to 10γ/ml added to the perfusion fluid were sufficient to inhibit completely the bronchial constrictive effect of 100γ of histamine diphosphate injected directly into the tracheal cannula. The injection of 1 mg of Antistine directly into the tracheal cannula only partially inhibited the action of the test dose of histamine.

Table I depicts the protection afforded guinea pigs against the toxic effects of an inhaled aerosol of histamine. The lower dose afforded considerable protection, which the higher dose augmented significantly. The end-point used was tetanic convulsions. These animals usually recovered if they were immediately removed from the chamber and injected subcutaneously with 0.1 mg per animal or epinephrine hydrochloride. The use of less severe symptoms as an "end-point" can prove deceiving. Dyspnea may develop which, even after fifteen minutes, has not been followed by convulsions despite a continued exposure to the histamine. Some animals may ultimately die after removal from the chamber without ever having exhibited convulsions. It may be noted that one animal in each dose-group failed to convulse after repeated exposure, despite a marked prolongation of the final exposure. This would suggest the development of some tolerance, a problem still subject to debate. In general, guinea pigs show a marked variation in their sensitivity to such fogs of histamine. These variables make an interpretation of the data obtained in this form of antihistamine assay difficult. The problems are enhanced if the atomizer employed produces a coarse spray instead of a stable fog.

TABLE II. THE PROTECTIVE ACTIONS OF ANTISTINE HCL AND PYRIBENZAMINE HCL AGAINST ANAPHYLACTIC SHOCK IN GUINEA PIGS

Antistine HCl					
Dose mg/kg	Pig No.	Survival Time, Minutes After Antigen	Dose mg/kg	Pig No.	Survival Time, Minutes After Antigen
28	1	6	42	1	15
	2	7		2	Survived
	3	17		3	44
	4	20		4	Survived
	5	15		5	12
	6	285		6	13
	7	12		7	Survived
	8	Died during night		8	18
	9	13			
	10	19			
Pyribenzamine HCl					
14	1	98	21	1	Died during night
	2	50		2	Died during night
	3	99		3	Survived
	4	16		4	Died during night
	5	88		5	Survived
	6	14		6	Survived
	7	30		7	Died during night
	8	16		8	Died during night
	9	30		9	15
	10	18			
Controls	1	9			
	2	5			
	3	3			
	4	3			
	5	3			
	6	3			

Anaphylaxis.—Table II summarizes the protective action in guinea pigs exerted by Antistine and Pyribenzamine against death from anaphylactic shock after the intravenous injection of a challenging dose of horse serum. This table has been included to emphasize the prolongation in the interval before death of those animals that succumbed. Table IIA summarizes the mortality data alone. The method of sensitization employed renders the animals acutely sensitive. The relatively poor protection afforded by even very high doses of the antihistamines would suggest one of three possibilities:

1. The precipitin titer is so high that the injection of the challenging dose of antigen causes the formation of multiple small emboli;

2. So much histamine is liberated by the antigen-antibody reaction that vascular shock is produced, as might well result, in view of the relatively poor protection that antihistamines afford against the hypotensive action of histamine;

3. Other toxic substances are liberated which the antihistamines do not antagonize. All of these factors may indeed play a role and perhaps others not mentioned. It is apparent from the results that Antistine is less effective than Pyribenzamine in preventing anaphylactic shock under the conditions of the experiment. This coincides with the report of Landau, Marriott, and Gay.[11]

TABLE IIA. EFFECT OF ANTISTINE HCL AND PYRIBENZAMINE HCL ON ANAPHYLACTIC SHOCK IN MALE GUINEA PIGS

Administered I. P. 30 Minutes Before Antigen

No. of Pigs	Antistine HCl			Horse Serum Dose cc	Route	No. of Deaths	% Mortality
	Dose mg/kg	Conc. %	Route				
10	28	2	IP	0.50	IV	10/10	100
8	42	2	IP	0.50	IV	5/8	62.5
	Pyribenzamine HCl						
10	14	2	IP	0.50	IV	10/10	100
9	21	2	IP	0.50	IV	6/9	66.6
6	Control Group			0.50	IV	6/6	100

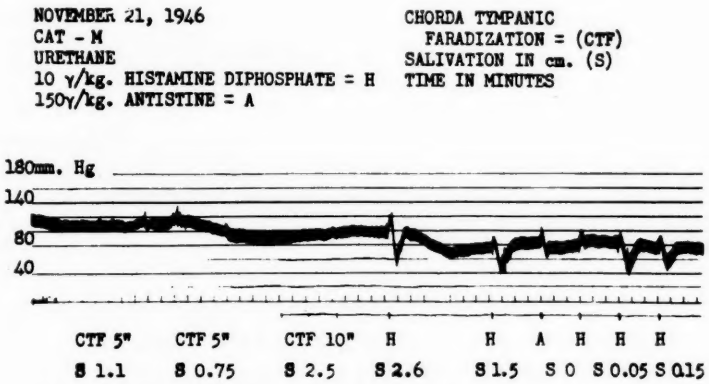


Fig. 3. Antistine in a dose of 150γ/kg injected intracarotidly may be seen to have eliminated the salivary response to 10γ/kg of histamine diphosphate given three minutes after the antihistamine. This inhibition was brief, as may be seen from the salivary responses to the subsequent two doses of histamine. The responses were slight but were increasing. The hypotensive response to the injected histamine may be seen also to have been diminished by the antihistamine.

Feline Salivation.—In six cats the action of Antistine injected intracarotidly in antagonizing the sialogogic action of histamine similarly injected was studied. Its antagonism toward the moderate stimulating effect of histamine upon the nictitating membrane was also investigated. Doses of 100 to 150γ/kg markedly inhibited or temporarily eliminated the salivary response to 10γ/kg of histamine diphosphate. The salivary responses to faradization of the chorda tympani or cervical sympathetic nerves were not altered by this dose of Antistine. The responses of the nictitating membrane to histamine were also inhibited but not as completely as were the salivary responses (Fig. 3).

Thiry-Vella Dogs.—Antistine was employed in six dogs with Thiry-Vella loops to antagonize the stimulating action on the intestine of doses of histamine that varied from 10γ to 20γ/kg. The doses of histamine were

varied because the dogs were not equally sensitive to histamine, and we wished to secure in each experiment a quantitatively similar intestinal response (Fig. 4).

In two of the six dogs a dose of 3 mg/kg of Antistine completely elimi-

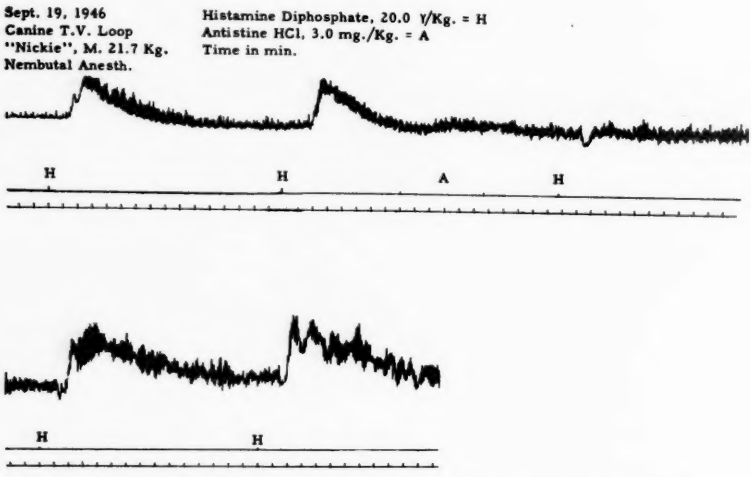


Fig. 4. 3 mg/kg Antistine may be seen to have eliminated for one trial the spasmogenic action on the intestine of 20γ/kg of histamine diphosphate.

nated the response to histamine. In a third dog, doses as low as 2 mg/kg were often effective. In the other three dogs, doses of 3 mg/kg proved insufficient, but that dose was not exceeded. In none of the six dogs did the doses employed give any evidence of untoward effects.

Histamine-Induced Hypotension.—Doses of from 1 to 5 mg/kg reduced the hypotensive action in anesthetized dogs of 5 to 10γ/ kg of histamine diphosphate by approximately a third. The injection of Pyribenzamine did not significantly augment the protective action afforded by previously injected Antistine. This is in agreement with the findings of Wells and his associates that antihistamines only partially protect against histamine-induced hypotension. Graham[9] has independently reported similar results with Antistine (Fig. 5).

Isolated Hearts.—Doses of from 10 to 50 γ injected directly into the aortic cannula caused moderate and brief inhibition of the kymographically recorded contractions of isolated, perfused hearts. The heart of the guinea pig was most sensitive to this inhibitory action, the hearts of the rabbit and the cat were least sensitive. Those of the rat and the hamster were intermediate in their responses.

Cerebrospinal Fluid Pressure.—The effects of Antistine upon the kymographically recorded spinal fluid pressure of ten cats were determined. Doses up to 10 mg/kg had little or no effect upon the cerebrospinal fluid pressure save for moderate changes that strictly paralleled the actions of

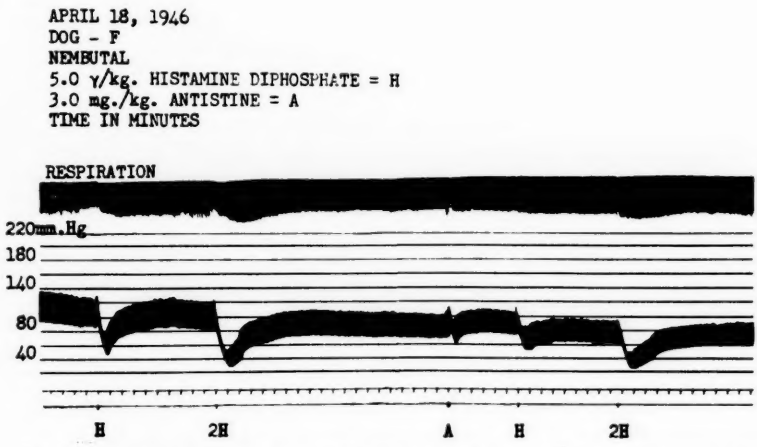


Fig. 5. 3 mg/kg Antistine may be seen to have diminished significantly the hypotensive response induced by histamine diphosphate. Complete inhibition by antihistamines of this action of histamine is seen only after the injection of very low doses of histamine.

the drug upon the blood pressure. The effects of histamine upon the CSF pressure were antagonized to the same extent as were the hypotensive effects of histamine.

Cilia.—Table III is a summary of the effects of Antistine sulfate and Pyribenzamine hydrochloride upon the ciliary activity of the frog's esophagus. The activity was followed for only sixty minutes, since it was recognized that any changes in ciliary activity occurring much after that time would be purely a reflection of the preparation's spontaneous deterioration, and also that a direct effect of the drug should become manifest within that interval.

TOXICOLOGY

Acute:

Rats: The LD_{50} as determined by the method of Behrens after rapid intravenous injections was 39 mg/kg.

Rabbits: 16 mg/kg intravenously caused convulsions and death in five of six approximately 3 kg rabbits.

Dogs: From investigations with seven dogs the following conclusions were reached: Doses up to about 8 mg/kg caused no symptoms after intravenous administration. Doses of from 8 to 15 mg/kg given intra-

TABLE III. EFFECTS OF ANTISTINE ON CILIA

Drug	No. of Determinations	Concentration*	Duration Ciliary Motility—Mins.
Pyribenzamine HCl	4	1:50	12
	4	1:100	15
	2	1:200	25
	4	1:300	30
	4	1:700	56
	4	1:1000 or less	60
Antistine Sulfate	4	1:50	6.5
	4	1:100	16
	4	1:250	26
	4	1:500	45
	4	1:1000 or less	60

*The perfusion fluid was 0.65% sodium chloride. For the various drug dilutions the mol fraction of added drug was calculated and the same mol fraction of sodium chloride was omitted from the fluid.

venously were followed by increasing degrees of apprehension, tremors, restlessness, salivation, hyperpnea, and emesis.

Salivation and emesis appeared only after the higher doses; 18 mg/kg proved fatal to one dog after severe convulsions. Such animals have been saved by the administration of chloroform or intravenous barbiturate to control the convulsions. After oral administration of the drug the following results were obtained: Doses of 10 mg/kg or less caused no symptoms. Doses of 15 to 30 mg/kg caused increasing restlessness and apprehension, with salivation and emesis after the highest dose. Doses of 40 mg/kg precipitated severe convulsions, which were successfully treated with chloroform or an intravenous barbiturate.

Chronic: These results have been previously reported in part.[6]

Rats tolerated 100 mg/kg per os five days a week for thirty days with no evidences of toxicity as adjudged by weight curves and hematological studies. Rats given 10 mg/kg per os five days a week for thirty days did not evidence tolerance or cumulative toxicity as adjudged by subsequent responses to the previously determined LD_{33} and LD_{83}. The gross autopsy of these rats revealed no abnormality nor did the subsequent histological examination of the following tissues: liver, kidney, adrenals, testes, and ovaries.[1]

WARBURG STUDIES

From 0.1 to 1 mg per ml Antistine hydrochloride caused 4 to 40 per cent inhibition of the oxygen uptake of hepatic slices from the rat. From 0.1 to 0.5 mg/ml Pyribenzamine hydrochloride caused from 7 to 28 per cent inhibition of the same tissue. Also, 0.3 mg/ml Pyribenzamine hydrochloride caused a definite but slight decrease in the oxygen uptake in experiments in which the same dose of Antistine hydrochloride caused no decrease. These experiments suggest that the Antistine is somewhat less toxic than the Pyribenzamine and that neither drug is toxic to this tissue save in relatively high doses.

DISCUSSION

The results of the foregoing investigations establish Antistine hydrochloride as an active antihistamine of low toxicity. The drug belongs to the group of antihistamines that do not potentiate the responses to epinephrine but rather inhibit those actions. Graham[10] reported that Neo-Antergan, one of the potentiating group, would, in higher doses, also inhibit the responses to epinephrine. This result has been confirmed by Löfgren.[12]

The observation was earlier made that the first dose of Antistine added to a bath containing isolated ileal strips from the guinea pig was frequently somewhat more effective in opposing a subsequent response to histamine than was any subsequent dose of the drug given after the control responses to histamine had been restored. This peculiarity we have not observed with other antihistamines, and we cannot explain it. It is structurally interesting that the nitrogen present in a straight chain in the antihistaminic compounds can be successfully replaced by a nitrogen present in a ring. This peculiarity is shared by at least one other antihistamine, N-methyl-N'-(4-chlorobenzhydryl) piperazine dihydrochloride (Compound No. 47-282), Chlorcyclizine, the properties of which were recently reported by Castillo, de Beer and Jaros.[5] The significance of these structural alterations must await further knowledge.

SUMMARY

The results of a study of 2-[phenylbenzylaminomethyl]-imidazoline hydrochloride (Antistine), an antihistamine, have been reported. The drug was shown to antagonize the spasmogenic action of histamine on intestinal muscle and on bronchiolar muscle. It antagonized the sialogogic effects of histamine. It partially antagonized the hypotensive action of histamine. It was shown to be an antihistamine of low toxicity, as evidenced by the results of both acute and chronic studies.

The authors thank Dr. James Leathem of Rutgers University for his report of the histological studies.

REFERENCES

1. Anderson, F. F.; Barrett, W. E., and Craver, B. N.: A multiple bath arrangement for studying the responses of isolated tissues. Arch. internat. de pharmacodyn. et de therap., 78:544, 1949.
2. Anderson, F. F., and Craver, B. N.: A pyrex apparatus for the perfusion of the coronary circulation of mammalian hearts. J. Pharmacol. & Exper. Therap., 93:135, 1948.
3. Barrett, W. E.: A method of studying ciliary motility by direct observation. Federation Proc., 6:307, 1947.
4. Barrett, W.: A method of sensitizing guinea pigs to horse serum that yields after challenging of the animals a 100% lethal response. To be presented at the Atlantic City Meetings of the Federation of American Societies for Experimental Biology, April, 1950.
5. Castillo, J. C.; de Beer, E. J., and Jaros, S. H.: A pharmacological study of N-ethyl-N'-(4-Chlorobenzhydryl) piperazine dihydrochloride—a new antihistamine. J. Pharmacol. & Exper. Therap., 96:388, 1949.
6. Craver, B.; Barrett, W.; Cameron, A.; Hays, H.; Holmquist, G.; Mackenzie, A., and Smith, J.: Pharmacological actions of 2-Phenylbenzylaminomethylimidazoline (Antistine). Federation Proc., 7:213, 1948.

7. Craver, B. N.; Cameron, A., and Smith, J.: Kymographic registration of cerebrospinal fluid pressure (in dogs and cats): effects of antihistaminics and common drugs thereon. Arch. internat. de pharmacodyn. et de therap., 80:310, 1949.
8. Craver, B. N.; Cameron, A., and Yonkman, F. F.: Comparative effectiveness of five antihistaminics vs. histamine-induced spasm in canine Thiry-Vella loops. J. Pharmacol. & Exper. Therap., 93:168, 1948.
9. Graham, J. D. P.: A comparison of some antihistamine substances. J. Pharmacol. & Exper. Therap., 91:103, 1947.
10. Graham, J. D. P.: Adrenaline inhibition by spasmolytic agents. J. Pharmacol., 1:17, 1949.
11. Landau, S. W.; Marriott, J. L., and Gay, L. N.: Comparative study of antihistamine substances. II. Activity *in vivo* against histamine intoxication and anaphylactic shock of guinea pigs. Bull. Johns Hopkins Hosp., 83:343, 1948.
12. Löfgren, L. B.: Antihistaminic substances and epinephrine action on blood pressure. Experientia, 5:409, 1949.
13. Mayer, R. L.; Brousseau, D., and Eisman, P. C.: Pyribenzamine aerosol inhalation and its influence on histamine poisoning and anaphylaxis. Proc. Soc. Exper. Biol. & Med., 64:92, 1947.
14. Meier, R., and Bucher, K.: Pharmakologie des 2-(N-phenyl-N-benzyl-aminomethyl) imidazoline (Antistin). Schweiz. med. Wchnschr., 76:294, 1946.
15. Tainter, M. L.; Pedden, J. R., and James, M.: Comparative actions of sympathomimetic compounds: bronchodilator actions in perfused guinea pig lungs. J. Pharmacol. & Exper. Therap., 51:371, 1934.
16. Wells, J. A.; Morris, H. C.; Bull, H. B., and Dragstedt, C. A.: Observations on the nature of the antagonism of histamine by β-dimethylaminoethyl benzhydryl ether (Benadryl). J. Pharmacol. & Exper. Therap., 85:122, 1945.
17. Yonkman, F. F.; Chess, D.; Mathieson, D., and Hansen, N.: Pharmacodynamic studies of a new antihistamine agent, N′-pyridyl-N′-benzyl-N-dimethylethylene diamine HCl, Pyribenzamine HCl. J. Pharmacol. & Exper. Therap., 87:256, 1946.
18. Yonkman, F. F.; Roth, F.; Smith, J.; Hansen, N., and Craver, B. N.: Local anesthetic properties of Antistine and Pyribenzamine hydrochloride. Anesth. & Analg., 28:170, 1949.
19. Yonkman, F. F.; Stillwell, D., and Jeremias, R.: The adrenolytic and sympatholytic actions of yohimbine and ethyl yohimbine. J. Pharmacol. & Exper. Therap., 81:111, 1944.

PREGNENOLONE ACETATE

(Continued from Page 33)

4. Freeman, H.; Pincus, G.; Johnson, C. W.; Bachrach, S.; McCable, G.; and MacGilpin, H.: Therapeutic efficacy of Δ^5-pregnenolone in rheumatoid arthritis. J.A.M.A., 142:1124, 1950.
5. Henderson, E.; Weinberg, M.; and Wright, W. A.: Pregnenolone. J. Clin. Endocrinol., 10:455, 1950.
6. Hoagland, H.: Adventures in biological engineering. Science, 100:63, 1944.
7. Ishmael, W. K.; Hellbaum, A.; Kuhn, J. F.; and Duffy, M.: The effects of certain steroid compounds on various manifestations of rheumatoid arthritis. J. Oklahoma State M. A., 42:434, 1940.
8. Pearlman, W. H., and Pincus, G.: The metabolism of pregnenolone. Federation Proc., 5:79, 1946.
9. Pincus, G., and Hoagland, H.: Effects of administered pregnenolone on fatiguing psychomotor performance. J. Aviation Med., 15:98, 1944.
10. Seifter, J.; Warter, P. J.; and Fitch, D. R.: Preliminary observations on the antiarthritic effect of 21-acetoxy-pregnenolone. Proc. Soc. Exper. Biol. & Med., 73:131, 1950.
11. Selye, H.: On the hormonal activity of a steroid compound. Science, 94:94, 1941.
12. Selye, H.: Correlations between the chemical structure and the pharmacological actions of the steroids. Endocrinology, 30:437, 1942.
13. Selye, H.: The pharmacology of steroid hormones and their derivatives. Rev. canad. de biol., 1:577, 1942.
14. Warter, P. J.: Cited by Henderson.[5]

Av. Rio Branco, 277

EFFECT OF ISUPREL ON ANTIGEN-ANTIBODY AND HISTAMINE SKIN REACTION

JOHN M. SHELDON, M.D., JOEL R. HUSTED, M.D., and ROBERT G. LOVELL, M.D.

Ann Arbor, Michigan

WITH the general acceptance of 1-(3,4, Dihydroxyphenyl)-2-isopropylaminoethanol Hydrochloride, known as Isuprel, Isonorin, Aludrine, or Isopropylepinephrine, the physician has been provided with another effective agent for symptomatic relief of bronchial asthma. This compound has the advantages over epinephrine of being effective when given sublingually as well as by injection and inhalation, and also, except perhaps for its effect on cardiac muscle, is less toxic than epinephrine.[3] Moreover, Gay[5] has reported clinical relief by use of Isopropylepinephrine in asthmatic patients who do not respond to epinephrine.

It is important with such a medication to evaluate its effect on the antigen-antibody and histamine skin reaction. Patients undergoing allergic investigation are routinely advised against taking an antihistaminic drug for twenty-four hours before diagnostic skin testing, since the antihistaminic drugs in general are felt to attenuate or obliterate the antigen-antibody reaction in the skin.[1,7,8] Feinberg,[4] however, observed that antihistaminic drugs obliterated dermographia in some patients with that condition who were being skin tested without appearing to alter the immunologic skin reaction. Aminophylline, given intravenously, likewise is said to reduce the size of wheals resulting from the intracutaneous antigen-antibody reaction.[10] This reduction in size of the skin reaction is comparable to, but not so great as, that resulting from the injection of epinephrine prior to testing. The allergist cannot assume that the effect of a medication always will be to reduce the size of the skin reaction. Ingestion of whiskey or grain alcohol will produce increase in the size, intensity and duration of the allergic wheal and erythema, regardless of the subject's clinical sensitivity to alcoholic beverage.[2]

Because of the close similarity in molecular structure between epinephrine and Isopropylepinephrine, one might suspect that the effect of both on the whealing reaction in the skin would be the same. However, the two compounds do not act with equal intensity pharmacologically,[6] and there is no justification in assuming that Isopropylepinephrine would inhibit the skin reaction to the same degree as does epinephrine. In fact, because of the lack in Isopropylepinephrine of the stimulating (pressor) action which is so strong in epinephrine, we might expect Isuprel to exert a different effect on the whealing reaction of the skin. This must be taken into consideration when doing diagnostic procedures on the allergic patient. It

From the Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan. Material furnished for this investigation by Winthrop-Stearns, Inc., New York 13, N. Y. This study has been made possible in part through the L. J. Montgomery Research Fund. With the technical assistance of Bette Lowe, R.N.

would be advantageous if it were possible to continue to administer Isopropylepinephrine during the skin testing procedure to the patient having mild asthmatic attacks which are annoying but not severe enough to warrant postponing the skin testing.

PROCEDURE

In order to clarify the picture, and to see what effect Isuprel has on the whealing reaction of the skin, a series of experiments was conducted. Allergic patients who had received no medication for at least twenty-four hours prior to consideration were skin tested to inhalant and ingestant antigens by single prick test technique. Results of the tests were measured at the end of twenty minutes, and were recorded. The patients were then given 10 mg Isuprel sublingually, and prick tests were repeated at ten minutes, in thirty minutes, and in some cases at the end of one and two hours.

Reactions were interpreted and recorded as follows: Erythema up to 21 mm in diameter = 1-plus; erythema larger in diameter than 21 mm = 2-plus; wheal (without pseudopods) and surrounding erythema of any size = 3-plus; wheal with pseudopods and surrounding erythema of any size = 4-plus. Readings of any one procedure were interpreted by the same individual.

Allergens used for prick test technique in these studies were concentrated antigen made from definite volumes and weights of protein material, prepared according to the technique of Straus and Spain,[9] and was used for testing in undiluted form. The antigen used for intradermal testing was a 1:10 dilution of the strongest material used in the hyposensitization of allergic patients, and was diluted from material in which the protein content was estimated by measurement of protein nitrogen.

A second group of allergic patients, similarly without medication for twenty-four hours, was skin tested by intradermal technique (after screening by prick test). Tests were read in twenty minutes as above and results recorded. Isopropylepinephrine 10 mg sublingually was then given and the intradermal tests were repeated, some within ten minutes (to allow for absorption), and others up to as long as thirty minutes and one hour after administration of Isopropylepinephrine. The tests were again read twenty minutes after application, and recorded.

Intradermal tests were also done in a third group of allergic patients without medication and results noted. Then Isopropylepinephrine 1:200 was placed in a DeVilbiss No. 40 nebulizer and the patients given six consecutive inhalations of spray from the nebulizer. Intradermal tests were then repeated immediately because of the rapid absorption of the medication, and in some patients at thirty and sixty minutes, and results again recorded as before.

Finally, in order to evaluate the effect of Isopropylepinephrine on the histamine-induced skin reaction, a group of non-allergic and allergic pa-

TABLE I

I. *Scratch Technique*

Antigen (concentrated) applied, skin scratched and tests read.* Isopropylepinephrine, 10 mg. sublingual) given. Using same allergen, test repeated in series at 10, 20, 30, 40 and 60 minutes and read.* Control of sterile buffered saline used in each patient.

Results:

No. of patients used for scratch tests	12
No. of series of skin tests done (scratch technique)	37
No. of series in which reaction was increased after Isopropylepinephrine	2
No. of series in which reaction was decreased after Isopropylepinephrine	6
No. of series in which reaction did not change after Isopropylepinephrine	29

II. *Intradermal Technique*

Antigen (various concentrations—1:50-1:5000) given intradermally. 0.05 cc and read.* Isopropylepinephrine (10 mg sublingually) given. Test repeated and read.* Control, 0.05 cc sterile buffered saline i.c. used in each patient.

Results:

No. of patients used for i.c. tests	12
No. of skin test series done (i.c. technique)	70
No. of series in which reaction was increased after Isopropylepinephrine	5
No. of series in which reaction was decreased after Isopropylepinephrine	41
No. of series in which no change observed after Isopropylepinephrine	24

III. *Intradermal Technique, Using Aerosol Isopropylepinephrine*

Antigen given as in (II) above, but instead of sublingual Isopropylepinephrine, aerosol solution 1:200 (six breaths with DeVilbiss No. 40 nebulizer), given before repeating tests. Control of saline given as above.

Results:

No. of patients used	9
No. of series of i.c. tests conducted	9
No. of tests which changed after Isopropylepinephrine	0

An additional patient had 4 allergens applied by scratch technique and was treated with 1:200 aerosol as above. No change recorded in his skin tests after medication.

IV. *Control Studies*

0.05 cc histamine in concentrations of 0.01 mg/cc; 0.001 mg/cc and 0.0001 mg/cc was given i.c. before and after Isopropylepinephrine (10 mg sublingual). Control of 0.05 cc buffered normal saline given in each case. Tests repeated after Isopropylepinephrine and read.*

Results:

No. of patients tested	19
No. of series of tests conducted (3 series per patient)	57
No. of series showing increase after Isopropylepinephrine	1
No. of series showing decrease after Isopropylepinephrine	2
No. of series showing no change after Isopropylepinephrine	52
No. of series impossible to interpret because of technique	2

V. *Control to Study Variation of Reaction in Testing Technique on Individual Patient*

0.05 cc of histamine in concentration of 0.01 mg/cc; 0.001 mg/cc; and 0.0001 mg/cc was given i.c. into the left arm of 13 patients, then the same procedure repeated in the right arm. Results were compared. Controls were run using 0.05 cc buffered normal saline.

Results:

In the 13 cases, in addition to control tests, a total of 39 pairs of tests were done and compared. A significant change in degree of reaction occurred in 5 of these tests, possibly being due to variation in technique of applying test to right and left arm; or to localized variation of skin response at the area tested.

*All tests read 20 minutes after allergen applied.

tients was subjected to intradermal injection of a series of dilutions of histamine acid phosphate before and after the administration of 10 mg of sublingual Isopropylepinephrine. All reactions were read twenty minutes after the injections were given. The histamine was injected at varying times from immediately up to as long as thirty minutes after the sublingual medication was given. Results were recorded.

A series of control injections was done to see how much variation occurred through technique, in the size, intensity, and duration of reaction when the same dose of histamine or allergen was given several times to the same patient.

RESULTS

There was no apparent significant alteration by sublingual Isopropylepinephrine of the skin reaction by prick technique. A "significant" change is regarded as the alteration of degree of reactivity as indicated by a change of one, two, three and four plus from the original recorded reading, measured twenty minutes after the allergen was applied and repeated on the same individual. The prick tests done before giving Isopropylepinephrine and those done after, agreed within experimental limits; and although in some cases there was observed some alteration in area of erythema and wheal size, in only eight tests of a total of thirty-seven tests conducted was the change sufficient to cause a change in recording of the test. A total of twelve patients were subjected to prick testing.

In the intradermal technique, however, there was definite attenuation and in some cases obliteration of the skin test by Isopropylepinephrine sublingually. The observation of a 4-plus intracutaneous reaction obtained prior to giving the drug, converting to a negative test after its administration, was made in a large number of cases. Twelve patients were used, and a total of seventy series of skin tests done. In forty-one of the seventy series, there was definite decrease in the degree of skin reaction. Nine patients tested by intracutaneous technique, then given Isopropylepinephrine 1:200 by nebulizer and re-tested, also showed definite attenuation of the size of the area of erythema and in some cases of the size of the wheal. In no case, however, was the change so great as to require changing the degree of reaction recorded.

Histamine-induced wheals were not significantly altered by sublingual Isopropylepinephrine. In some cases there was alteration of the area of erythema or the size of the wheal, but these changes were not so great as to be unexplained by variation in experimental technique, when compared with the series of control injections made for this purpose.

DISCUSSION

Administration of Isopropylepinephrine sublingually apparently has little practical clinical effect in altering the whealing reaction by cutaneous or scratch technique in which a concentrated allergen is used, and where results are measured and recorded as described above.

A definite alteration and even obliteration of the intradermal skin test may occur after giving Isopropylepinephrine sublingually when results are measured and recorded according to the 1-plus to 4-plus criteria outlined above, and the antigens used are 1:10 dilutions of the full-strength stock standardized solution. The degree of change in reaction was much greater in some patients than in others, suggesting that in certain patients Isopropylepinephrine may exert more influence on the skin response than in others.

Aerosol Isopropylepinephrine, although it may attenuate the intradermal

skin reaction when performed as outlined, did not alter the degree of reaction sufficiently to change its interpretation for recording.

All effects of Isopropylepinephrine on skin tests appeared to have worn off in less than two hours.

SUMMARY

Isopropylepinephrine, a sympathomimetic drug very similar to epinephrine, is now accepted as a useful drug in treatment of allergic diseases. Like epinephrine, it appears to influence the degree of whealing response of the skin, particularly to the intracutaneous test where a more dilute antigen is used. Little if any significant alteration of the whealing response was demonstrated by prick technique where a concentrated antigen was used. Isopropylepinephrine also caused little change in the histamine-induced dermal reaction.

The allergist performing skin tests, especially by intradermal technique, should withhold Isopropylepinephrine for several hours before and during skin testing procedures, since this drug, like epinephrine and aminophylline, may alter the skin test result, particularly in certain patients whose reactions to allergen testing seem to be influenced greatly by Isopropylepinephrine.

REFERENCES

1. Criep, L. H., and Aaron, T. H.: Neohetramine: an experimental and clinical evaluation in allergic states. J. Allergy, 19:215, 1948.
2. Dees, S. C.: An experimental study of the effect of alcohol and alcoholic beverages on allergic reactions. Ann. Allergy, 7:185, 1939.
3. Dertinger, B. L.; Beaver, D. A., and Langs, A. M.: Toxicity of 1-(3,4,dihydroxyphenyl)-2-isopropylaminoethanol hydrochloride. Proc. Soc. Exper. Biol. & Med., 68:501, 1948.
4. Feinberg, S. M.: Allergy in Practice. Second ed., p. 809. Chicago: Yearbook, 1946.
5. Gay, L. N., and Long, J. W.: Clinical evaluation of Isopropylepinephrine in management of bronchial asthma. J.A.M.A., 139:452, 1949.
6. Gilman, A.: The pharmacology of drugs used in allergic conditions. J. Allergy, 19:281, 1948.
7. Schwartz, E., and Wolf, J.: Histamine antagonists. A comparative study of their effect on histamine and allergic skin wheals. J. Allergy, 20:32, 1949.
8. Serafini, U.: Studies on histamine and histamine antagonists. J. Allergy, 19: 256, 1948.
9. Straus, M. B., and Spain, W. C.: Laboratory procedures. In Cooke, R. A.: Allergy in Theory and practice. P. 527. Philadelphia: W. B. Saunders, 1947.
10. Tuft, L., and Brodsky, M. L.: Influence of various drugs upon allergic reactions. J. Allergy, 7:238, 1936.

Department of Internal Medicine
University of Michigan Medical School

ERRATUM

In the paper by Bernard Berkowitz and Morris Scherago entitled "Standardization of Dust Extracts. II. *In Vitro* Leukocytolysis in the Assay of the Allergenicity of Dust Extracts," which appeared in the July-August, 1950, issue of ANNALS OF ALLERGY, Figures 1 and 2 are reversed. Figure 1 on page 459 is actually Figure 2, and likewise Figure 2 on page 462 should have been Figure 1.

THE USE OF ANTIHISTAMINIC DRUGS IN THE TREATMENT OF EPIDERMOPHYTOSIS OF THE FEET AND EPIDERMOPHYTIDS

A Preliminary Report

ELIZABETH AUSTIN, M.D.
Los Angeles, California

WITH promise of symptomatic relief for allergic manifestations which antihistaminic drugs bring, a review of the allergic aspects of fungus infections of the feet was made to determine whether or not these drugs might present a new method of treatment for the prevalent condition popularly known as "athlete's foot," and clinically as epidermophytosis.

The relationship of mycology and allergy has been studied extensively, particularly relating to asthma and molds,[1,2,3,5,8] and the production of atopic eczema by molds was noted by Feinberg[4] in 1939.

The allergic aspects of epidermophytosis of the feet and epidermophytids of the hands was extensively reviewed and supplemented by Peck.[7] By experimental reproduction of the disease syndrome in a volunteer he was able to demonstrate the sensitization of the patient by one episode of epidermophytosis and the allergic aspects of reinfection, including a shortened incubation period, shorter course, and more generalized reaction. Fungi were more difficult to find. Epidermophytids followed reinfection as an allergic phenomenon. This author and others have stressed the demonstration of the state of allergy by means of intracutaneous trychophyton tests, producing a local positive reaction in all cases.

Peck,[7] comparing the histological appearance of fungus disease as manifested by the primary vesicle of the skin with those diseases of known allergic etiology, states that the histological character of the vesicular epidermophytids is identical with the primary mycotic dysidrosis of the feet except for the absence of fungi. An analogous mechanism exists in the eczematoid reaction. Clinically and histologically the epidermophytid reaction is identical with eczema. "It differs from allergic eczema caused by foods and medicaments only by the origin of the allergen (fungus), not, however, in allergic pathogenesis and still less in its clinical and histological manifestations."[7]

The very diversity of the manifestations of allergy suggests that a common factor such as histamine plays a prominent role in producing allergic manifestations. In 1937, Sir Thomas Lewis[6] observed that the skin responds to mechanical, thermal, electrical, and chemical stimuli by the production of a wheal with surrounding erythema. He further noted the production of a wheal following the introduction of specific protein antigen into a sensitized skin site. He postulated that all responses of this type were not produced by the stimulus directly, but were the result of a liberation of a diffusible substance from the injured cell, indistinguishable from histamine.

Material supplied by the Department of Therapeutic Development, Parke, Davis & Co.

Peck[7] noted that fungi could be cultured from plantar lesions without difficulty but that positive cultures were found less frequently in other lesions on the feet and practically never from id reactions on the hands. It is possible, therefore, that vesicles occurring on the feet with negative findings may be on an allergic basis—epidermatophytids.

It was postulated that an antihistaminic drug should be tried on epidermophytosis to see whether it might be a clinically efficient method of dealing with a difficult problem. Benadryl* was selected.

Thirty acute clinical cases were chosen, and fifteen of these were used as controls and treated with the usual methods. The controls cleared slowly over a period of two weeks to several months, and four have had intermittent itching and interdigital scaling, three have had one recurrence with vesicle formation and marked pruritus, three have had two such episodes, and five have been symptom free.

Patients under treatment with Benadryl were given 50 mg three times daily. The only side reactions noted were mild sleepiness in two patients. All cases showed mycelia with standard preparations. Six are presented here.

CASE REPORTS

Case 1.—Miss A. W. presented generalized scaling from chronic epidermophytosis with an acute flare-up. Three pustules of one week's duration were present on the plantar surface of the right heel. There was generalized irritation from home medication with salicylic acid preparation. A low pain threshold aggravated pruritus, and there was a complicating hyperdrosis of both feet and hands.

Local treatment consisted of opening the pustules and applying a dry sterile dressing. Benadryl 50 mg three times daily was given for two days. When the patient returned at that time, she stated that the itching had stopped one hour after taking the first capsule of Benadryl and that there had been a marked diminution of hyperdrosis.

The pustules were almost healed. Benadryl was continued for three more days—five days' treatment in all—and at the end of that time there remained only a light scaling of the skin. There has been no recurrence in nine months.

Case 2.—Mrs. C. A. presented acute generalized epidermophytosis of both feet with pustules on the plantar surfaces and had in addition epidermophytids on both hands. The pustules were opened and covered with a dry sterile dressing. Benadryl was prescribed for two days, then for five days more. At the end of seven days both epidermophytosis and epidermophytids were drying, and pruritis had been absent since the first day. The drug was then continued for five more days. One month later the lesions on both hands and feet were completely healed, and there has been no recurrence in seven months.

Case 3.—Mr. A. had had chronic epidermophytosis on both feet for one year with mild pruritus. Benadryl was prescribed for three days. Five days later the patient stated that the pruritus had subsided the first day. The lesions were drying rapidly. Two weeks later all lesions were gone, and patient has been symptom free for six months.

*Parke, Davis and Company. Formula: beta-dimethyl amino-hydryl ether hydrochloride.

Case 4.—Mr. J. G. had chronic epidermophytosis with scaling on the plantar surface of both feet, and there was vesicle and pustule formation on the left foot with intense itching. Epidermophytids were present on both hands. The patient had been treated for the same complaints at intervals since 1945. The pustules and vesicles were opened and then dressed with dry sterile dressings after a magnesium sulfate soak. Benadryl given for three days resulted in subsidence of pruritus. The drug was repeated for another five days. Eleven days after treatment was begun the feet were entirely clear of all epidermophytosis, and the epidermophytids were almost gone. Eight months later there had been no recurrence.

Case 5.—Mr. N. C. complained of acute epidermophytosis with intense itching. Benadryl was prescribed for three days. At that time the patient reported that pruritus stopped one-half hour after taking the drug. The lesions were drying. One month later, without further medication of any kind, the skin was normal and there had been no return of symptoms. The patient was symptom free eight months later.

Case 6.—Mrs. H. R. had acute epidermophytosis in the third and fourth interdigital spaces with marked pruritus and generalized hyperdrosis on the feet, particularly interdigitally. Compound tincture of benzoin with 10 per cent salicylic acid was prescribed for local application to the affected areas. Two weeks later the fungus infection had not improved and the patient still complained bitterly of the itching. The local application was stopped, and Benadryl was prescribed for four days. Pruritus was absent two days later. Two weeks later the skin was normal and hyperdrosis was absent. There has been no recurrence in six months.

The most noticeable subjective effect of this drug was relief from pruritus, occurring from thirty minutes to two days after medication was begun. Following relief of pruritus, there was usually a rather marked decrease in hyperdrosis, if present.

Objectively the inflammation and vesicle formation of both epidermophytosis and epidermophytids were reduced in from two to fifteen days, depending upon the extent of the involvement. Drying of the vesicles helped to remove the media for proliferation of the fungi and lessened the chance of mechanical spread to other areas. Furthermore, when the areas involved presented a complicating overtreatment dermatitis, this medication was ideal, for local treatment could be cut to a minimum or eliminated.

SUMMARY

The clinical and histological relationship of mycology and allergy has been noted, and the histamine-like response of the skin to fungus infection has been discussed.

Benadryl 50 mg three times daily was used in a small series of cases to determine whether antihistaminic agents might prove to be useful in treating epidermophytosis and epidermophytids.

Results were satisfactory in this small series as compared with a control series of equal number. Pruritus was relieved in thirty minutes to two days, hyperdrosis was controlled well, and vesicles showed drying in two

(Continued on Page 59)

EVALUATION OF SOLID ("DUST") AEROSOLS AS THERAPEUTIC AGENTS

MAURICE S. SEGAL, M.D., F.A.C.A., HYMAN J. RUBITSKY, M.D., ELLIOTT BRESNICK, M.D., and LEON LEVINSON, M.D.

Boston, Massachusetts

AEROSOLS are suspensions of finely divided particulate matter in a gaseous medium. The particles may be either liquid, as in fog, or solid, as in smoke. The therapeutic value of liquid aerosols has become firmly established. We have recently evaluated the various liquid aerosols of sympathomimetic amines commonly employed for the management of bronchospasm.[1,10] Liquid aerosols of penicillin and streptomycin are of value in the management of various types of bronchopulmonary sepsis.[11]

Interest in the use of solid rather than liquid aerosols stems from the development of various types of suitable apparatus by Taplin[14] and Krasno[5] and their colleagues in 1947. All of these apparatus consist basically of devices by which small quantities of a micro-pulverized solid (average particle diameter approximately 1.0 micron) are shaken into an air stream and inspired. Reports have now appeared dealing with dusts of penicillin,[4,16] streptomycin,[16] diphenhydramine,[15] isopropylepinephrine[3] and aminophyllin.[17] In this communication we shall present laboratory data which may serve as a basis for evaluation of the therapeutic potency of these dusts.

SOLID AEROSOLS OF BRONCHOSPASMOLYTIC AGENTS

These preparations have been studied by means of a human assay technique which has been reported in detail elsewhere.[6] In brief, the test is based on changes in the vital capacity of asthmatic subjects induced by a bronchospastic agent, both prior to and following the administration of a therapeutic ("protecting") drug. In these studies, determination of the vital capacity was made before, and one-half, one and two minutes after the intravenous administration of either histamine diphosphate* or methacholine chloride.** A consistent reduction of 1000 cc or of at least 25 per cent of the resting vital capacity was first obtained and usually repeated prior to the administration of the "protecting" drug to be tested. We have found that relatively constant decreases, varying only 100 to 200 cc, can be obtained at intervals of one-half hour for six to seven hours. Each

From the Department of Inhalational Therapy, Boston City Hospital, and the Department of Medicine, Tufts College Medical School. Aided by a grant from the United States Public Health Service.

Dr. Segal is director, Department of Inhalational Therapy, Boston City Hospital; Clinical Professor of medicine, Tufts College Medical School.

Dr. Rubitsky was formerly a resident in medicine, Department of Inhalational Therapy, Boston City Hospital.

Dr. Bresnick is an assistant in medicine, Tufts College Medical School.

Dr. Levinson is an assistant in medicine and instructor in physiology, Tufts College Medical School; Associate Fellow of the American College of Allergists.

*Kindly supplied by Abbott Research Laboratories, North Chicago, Illinois.

**Kindly supplied by Merck and Company, Rahway, New Jersey.

subject thus serves as his own control in each experiment, obviating further consideration of the day-to-day fluctuations in the individual's vital capacity and in his sensitivity to the bronchospastic agent.

We have defined "protection" as that percentage of the control fall in vital capacity which persists after a particular therapeutic agent has been administered. The formula

$$P = \frac{C - E}{C} \times 100$$

has been employed, where P is the degree of protection afforded in per cent, 100 per cent indicating absence of any decrease in vital capacity after administration of the bronchospastic agent), C is the control decrease in vital capacity produced by the same dose of the bronchospastic agent before administration of the protecting drug, and E represents the decrease similarly produced at any given time after the latter had been given. It has repeatedly been shown that the results of any one protection study in a single individual may have little general applicability. We have, therefore, averaged the results obtained in several (at least four) patients into each curve. Protection is regarded as significant only when it is 40 per cent or more, to allow for variations in subjects and technique.

Aminophyllin and diphenhydramine dusts were nebulized by means of a simple inhaler consisting of two cylinders of transparent plastic which may be screwed together, and which contain within them a hollow cylindrical well into which may be placed a standard gelatin capsule.† By removing or perforating the top of the capsule and compressing the small rubber bulb attached to the inhaler, the powder may readily be nebulized. The dose of aminophyllin was 260 mg; of diphenhydramine, three inhalations of a 25 per cent powder. The isopropylepinephrine dust was nebulized in the device described by Krasno et al,[3,4,5] in which the dust, contained in a detachable plastic cartridge with a fine mesh wire screen at the bottom, was released in small amounts into a discharge chamber by the impacts of an aluminum ball that struck the cartridge with each inhalation.

The most frequent complaint observed with aminophyllin and diphenhydramine "dusts" was a bitter taste. Most patients obtained pharyngolaryngeal anesthesia after inhaling the diphenhydramine powder. With three inhalations of isopropylepinephrine dust, all patients experienced some weakness, palpitation and giddiness. Several complained of slight headache, and one patient suffered a bout of paroxysmal auricular tachycardia.

The antihistamine and antimethacholine protecting potencies of these preparations are presented in Figures 1 to 3.

Administration of 260 mg of aminophyllin as a solid aerosol yielded

†Kindly supplied by the Upjohn Company, Kalamazoo, Michigan.

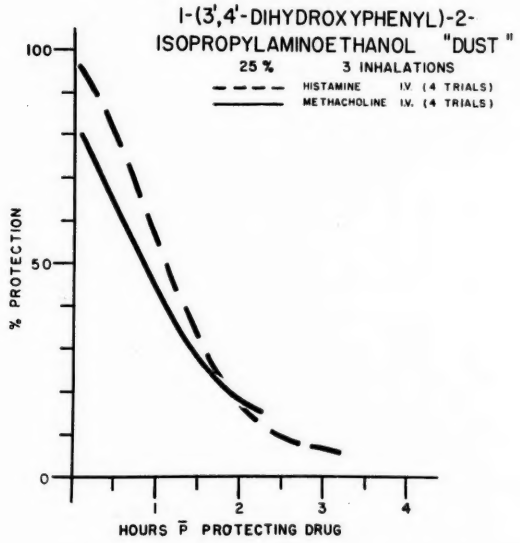


Fig. 1. Protective capacity of three inhalations of a dust containing 25 per cent isopropylepinephrine (1-(3',4'-dihydroxyphenyl)-2-isopropylaminoethanol) powder against the drop in vital capacity induced by intravenous histamine or methacholine.

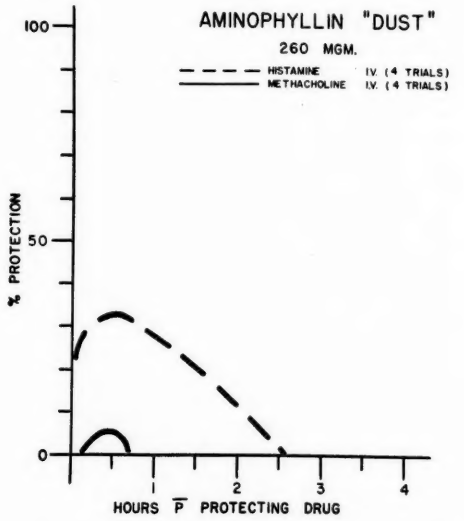


Fig. 2. Protective capacity of 260 mg of micropulverized aminophyllin, administered as a solid aerosol, against the drop in vital capacity induced by intravenous histamine or methacholine.

no significant protection against the decrease in vital capacity induced by histamine or by methacholine. These results are in accord with our previously reported data on liquid aminophyllin aerosols[11] and conflict with the findings of other investigators, who employed different apparatus and techniques.[7,17]

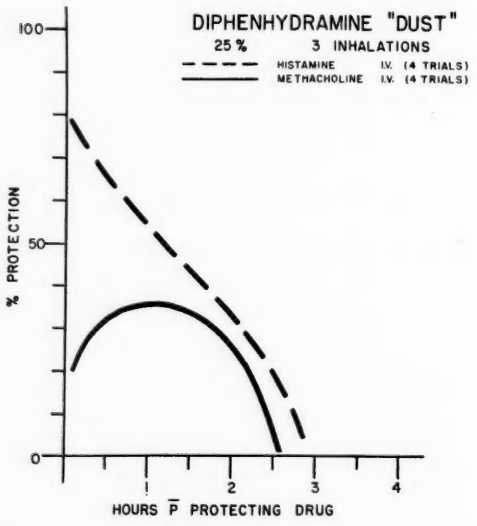


Fig. 3. Protective capacity of three inhalations of a dust containing 25 per cent diphenhydramine powder against the drop in vital capacity induced by intravenous histamine or methacholine.

Three inhalations of diphenhydramine dust conferred striking immediate protection against histamine, with a level of 79 per cent five minutes after the inhalations. Significant degrees of protection lasted ninety-five minutes. These figures would have been even higher were it not for the poor protection repeatedly observed in one of the patients studied (A.N.). No significant protection against methacholine was observed. These data again are roughly comparable to results obtained with liquid diphenhydramine aerosol.[9] Inhalation of diphenhydramine dust leads to pronounced hypesthesia, even anesthesia, of the oral and pharyngeal mucous membranes. This does not occur with the liquid aerosol.

Three inhalations of isopropylepinephrine dust yielded almost complete immediate protection against histamine (96 per cent) and methacholine (80 per cent). The duration of significant protection was eighty and sixty-six minutes, respectively. The side reactions following the administration of this dust were those of excessive cardiovascular stimulation. Both the protective abilities and the side reactions are comparable to those following

TABLE I. BLOOD LEVELS AND URINARY EXCRETION FOLLOWING ADMINISTRATION OF ANTIBIOTIC "DUST" AEROSOLS

Agent and Route	Blood (units/cc)								Urine
	½ hour		1 hour		2 hour		4 hour		24 hour Total
	Average	% Positive*	Average	% Positive*	Average	% Positive*	Average	% Positive*	
Crystalline Penicillin G 100,000 Units (10 trials)	0.18	100	0.10 (83% "positive" sera in first 2 hours)	90	0.04	60	0.01	10	21,750
Procaine Penicillin G 100,000 Units (10 trials)	0.11	80	0.09 (60% "positive" sera in first 2 hours)	70	0.03	30	0.01	20	12,220
Dihydrostreptomycin Sulfate 100 mg (5 trials)	0.31		0.19		0.31		0.21		570

*Greater than 0.04 units per cc (penicillin only). Combined apparatus and mouth wash loss ranged from 4 to 8 per cent with penicillin and from 3 to 35 per cent with streptomycin.

the administration of six inhalations of a liquid aerosol of 1 per cent isopropylepinephrine.[1]

SOLID AEROSOLS OF ANTIBIOTIC AGENTS

To study the efficacy of the administration of penicillin and streptomycin as solid aerosols,[13] we have determined the blood levels and urinary excretion following single doses of these agents to a group of normal middle-aged male volunteers. These dusts were administered in the same way as described above for aminophyllin and diphenhydramine dusts. The results are presented in Table I.

It is apparent that administration of solid aerosols of penicillin produces blood levels comparable to those which follow liquid penicillin aerosolization,[12] and which equal or surpass the minimum therapeutic level of 0.04 units per cc of serum, after the aerosol administration of a single dose of 100,000 units. Somewhat higher levels are found after administration of streptomycin in the same dose. The therapeutic significance of the streptomycin blood levels is less certain. Procaine penicillin G yielded lower blood levels and urinary excretion than did crystalline penicillin G. No prolongation of effect with procaine penicillin was noted in these studies.

DISCUSSION

The administration of solid aerosols of aminophyllin, diphenhydramine, isopropylepinephrine, penicillin, and streptomycin yield effects comparable in each case to the administration of the same agents as liquid aerosols.

The three dusts of bronchospasmolytic agents seem to offer no particular advantage over liquid aerosols of the same agent, and there are certain definite disadvantages. Aminophyllin aerosols of both types (solid and liquid) are ineffective in preventing the drop in vital capacity induced by histamine or methacholine. The anesthesia which follows the administration of diphenhydramine dust is distressing to the patient and may possibly

indicate ciliary paralysis, a development to be avoided in the management of bronchial asthma. The side reactions after isopropylepinephrine dust are of such magnitude as to suggest the possibility of fatal overdosage when the material is employed for self-medication.

The situation with regard to solid aerosols of antibiotic agents is somewhat different. The powder inhaler allows the administration of significant doses of penicillin or streptomycin quickly and easily, without the use of compressed air or oxygen as is practically essential with liquid antibiotic aerosols due to the comparatively large volume of solution which must be dispersed. The danger of sensitivity reactions following the use of dusts of penicillin or streptomycin is greater than with liquid aerosols, however, because of the high concentration of these agents present upon solution of the dust particles in the tracheobronchial mucus. Both penicillin and streptomycin dusts may act as nonspecific pharyngeal irritants. Allergic reactions have been observed by others in 5 to 6 per cent of patients treated with penicillin dust.[2] Individuals who exhibit sensitivity to penicillin G may be treated with penicillin O, a preparation described as effective in such patients, and to which no sensitivity reactions have been observed.[2]

SUMMARY

1. Aerosols composed of finely divided solid particles of aminophyllin, diphenhydramine, and isopropylepinephrine have been evaluated in terms of their ability to prevent the decrease in vital capacity induced in sensitive asthmatic subjects by histamine and methacholine. In each case the solid aerosol yielded results comparable to liquid aerosols: aminophyllin was ineffective against either bronchospastic agent, diphenhydramine was an excellent antihistamine, and isopropylepinephrine protected against both histamine and methacholine. The topical anesthesia following diphenhydramine dust and the cardiovascular stimulation following isopropylepinephrine dust render them less valuable for the control of bronchospasm than their liquid aerosol counterparts.

2. Similar solid aerosols of penicillin and streptomycin were assayed in terms of blood levels and urinary excretion. Again results similar to those which follow the administration of liquid aerosols were obtained These dusts are easier to administer but more likely to produce sensitivity reactions than are liquid aerosols of the same agents.

REFERENCES

1. Bresnick, E.; Beakey, J. F.; Levinson, L., and Segal, M. S.: Evaluation of therapeutic substances employed for the relief of bronchospasm. 5. Adrenergic agents. J. Clin. Investigation, 28:1132, 1949.
2. Burbidge, E.: Personal communication.
3. Krasno, L. R.; Grossman, M. E., and Ivy, A. C.: The inhalation of 1-(3′,4′-dihydroxyphenyl)-2-isopropylaminoethanol (Norisodrine sulfate) dust. J. Allergy, 20:111, 1949.
4. Krasno, L. R.; Karp, M., and Rhoads, P.: The inhalation of penicillin dust. J.A.M.A., 138:344, 1948.

5. Krasno, L. R.; Karp, M., and Rhoads, P.: The inhalation of penicillin dust. Science, 106:249, 1947.
6. Levinson, L.; Beakey, J. F.; Bresnick, E., and Segal, M. S.: Evaluation of therapeutic substances employed for the relief of bronchospasm. 2. Historical development and methods. Ann. Allergy, 6:705, 1948.
7. Prigal, S. J.; Brooks, A. M., and Harris, R.: The treatment of asthma by inhalation of aerosol aminophyllin. J. Allergy, 18:16, 1947.
8. Rubitsky, H. J.; Bresnick, E.; Levinson, L.; Risman, G., and Segal, M. S.: Parenteral and aerosol administration of antihistaminic agents in the treatment of severe bronchial asthma. New England J. Med., 241:853, 1949.
9. Rubitsky, H. J.; Levinson, L.; Bresnick, E.; Risman, G., and Segal, M. S.: The variability of oral antihistaminic therapy. Ann. Allergy, 8:536, 1950.
10. Segal, M. S.; Beakey, J. F.; Bresnick, E., and Levinson, L.: A comparative study of the action of various sympathomimetic amine aerosols in counteracting the dyspnea and bronchospasm induced by histamine and by acetyl-beta-methylcholine. J. Allergy, 20:97, 1949.
11. Segal, M. S.; Levinson, L.; Bresnick, E., and Beakey, J. F.: Evaluation of therapeutic substances employed for the relief of bronchospasm. 6. Aminophyllin. J. Clin. Investigation, 28:1190, 1949.
12. Segal, M. S.; Levinson, L., and Miller, D.: Penicillin inhalation therapy in respiratory infections. J.A.M.A., 134:762, 1947.
13. Segal, M. S.; Rubitsky, H. J.; Mellen, D. J., and Levinson, L.: Penicillin and streptomycin "dust" aerosols. Bull. New England M. Center, 11:210, 1949.
14. Taplin, G. V., and Bryan, F. A.: The administration of micronized therapeutic agents by inhalation or topical application. Science, 105:502, 1947.
15. Taplin, G. V., and Bryan, F. A.: The use of micronized therapeutic agents by inhalation with special reference to allergic pulmonary conditions. Ann. Allergy, 6:42, 1948.
16. Taplin, G. V.; Cohen, S., and Mahoney, E.: Prevention of postoperative pulmonary infection by inhalation of micropowdered penicillin and streptomycin. J.A.M.A., 138:4, 1948.
17. Taplin, G. V.; Gropper, A. L., and Scott, G.: Micropowdered aminophyllin or theophylline inhalation therapy in chronic bronchial asthma; evaluation by recorded vital capacity changes. Ann. Allergy, 7:513, 1949.

370 Commonwealth Ave. (Segal)

ANTIHISTAMINIC DRUGS IN THE TREATMENT OF EPIDERMOPHYTOSIS

(Continued from Page 52)

to eleven days. It was felt that relief of pruritus and the rapid drying of the affected areas decreased the factor of mechanical dissemination.

Further studies relative to the usefulness of antihistamines in the treatment of epidermophytosis and epidermophytids are indicated.

REFERENCES

1. Brown, G. T.: Sensitization to fungi. Ann. Int. Med., 6:655, 1932.
2. Cadman, F. T.: Asthma due to grain rust. J.A.M.A., 83:27, 1924.
3. Feinberg, S. M.: Mold allergy: its importance in asthma and hay fever. Wisconsin M. J., 34:254, 1935.
4. Feinberg, S. M.: Seasonal atopic dermatitis: role of inhalant atopens. Arch. Dermat. & Syph., 40:200, 1939.
5. Feinberg, S. M.: Seasonal hay fever and asthma due to molds. J.A.M.A., 107:1862, 1936.
6. Lewis, Thomas: Blood Vessels of Human Skin and Their Responses. New York: The Macmillan Company, 1927.
7. Peck, S. M.: Epidermophytosis of the feet and epidermophytids of the hands. Clinical, histological and experimental studies. Arch. Dermat. & Syph., 22: 40, 76.
8. Van Leevwen, V. S.: Proc. Roy. Soc. Med., 17:19, 1924.

1400 N. Vermont Avenue

THE ROLE OF THE QUESTIONNAIRE IN THE DIAGNOSIS OF ALLERGIC CONDITIONS

ETHAN ALLAN BROWN, M.D., F.A.C.A.
Boston, Massachusetts

THOSE of us who over the years see increasingly large numbers of allergic patients are faced with a series of serious problems. Increasing demands upon us for what may be termed medical-social activities are the cause of pressure and loss of time in an era of rising costs. There is a limited amount of energy any of us, however skillful, can give to any one patient, and there is the stubborn fact that, however well endowed our investigative sense may be, we do not and cannot always remember to ask all of the necessary questions. When we do, the patient does not, at the moment, know the necessary answers. Is there, therefore, any part of our job that we can deputize and, if necessary, which part and to whom?

Skillful technicians can do a great deal of our laboratory work. Junior physicians can be trusted to do physical examinations. The taking of the history, however, is an activity in which we prove ourselves to be experts. The patient's posture, speech and pattern of thought are all part of the history and cannot be obtained secondhand. Although there is a large part of the history which we must obtain directly from the patient, and by ourselves, there are other parts, consisting of questions to which the patient does not know the answers, or to which the answers can more easily be procured outside the office. In the last decade, a number of successive questionnaires have been prepared, which, although by no means perfect, enable us to obtain a large amount of accurate information with the expenditure of little time and energy.

The questionnaire for patients with respiratory system allergy consists of approximately 100 questions, following a purposefully simple introduction. This can be handed to any patient whose ability to answer the questions can be trusted. It is extremely useful in foreign-born patients, who themselves do not talk English, but frequently have members of their families who speak the language sufficiently well to furnish the requisite information.

The patient has merely to encircle or underline the appropriate response as "Yes" or "No." A cross placed before or after a question signifies that it does not apply.

It can be seen from the copy of the first page of the questionnaire that the questions listed pertain to the nose and throat and help differentiate the conditions of the skull which might show themselves as acute or chronic infection, physicial abnormalities, or defects of the nose and sinuses. They probe into the possibility of brain tumor, glaucoma, migraine, visual defects, hypertension, and simple psychological tension headaches as well

Physician-in-Chief, Allergy Section, New England Medical Center, Boston, Massachusetts; Director, Asthma Research Foundation, Inc., Boston, Massachusetts.

as the usual allergic manifestations of the nasal and pharyngeal areas. These first twenty questions supplement the physician's own preliminary history, corroborating his findings as to whether the condition is acute or chronic, mild or severe, seasonal or perennial, environmental or non-environmental, and also whether it is associated with other abnormalities or nonspecific irritations, which might possibly be forgotten or minimized.

The second page is concerned, in part, with important allergic and non-allergic throat conditions, eliciting the possibility of irritation from smoking and early carcinoma, bronchiectasis, a chronic heart or lung abnormality, or a hiatus hernia. Increase in weight due to edema will be discovered before there are any obvious clinical signs. Nonspecific factors are listed in the forty-ninth question, a most important finding in most histories.

The third page of the questionnaire continues with questions regarding coughs and their progress into asthma. Questions 50 to 60 indicate severity and the possibility of environmental factors, emotional causes, and physical allergy. The fifty-seventh question brings up the possibility of a pedunculated thyroid adenoma. Physicial and environmental, barometric, seasonal, infectious and emotional factors are all included, as are the results of previous studies and injection therapy.

The fourth page of the questionnaire winds up the history by eliciting such information as may lead to a better physical examination. By the time the patient has answered the ninetieth question, he has helped to rule out bronchial infection, carcinoma, and heart and kidney disease as they may affect the lung. The last two questions refer fleetingly to atopic eczema, urticaria, and drug sensitivities as well as to immediate and remote familial allergy.

The average patient has no difficulty whatsoever in answering these questions, and the information in the patient's own handwriting has medico-legal implications, as, for instance, in compensation claims where it sets the date at which symptoms were, or were not, present.

A second questionnaire, the Food Check List, has been found most useful in ruling out the more obvious effects of alimentary food allergens. It was written for the patient and is simple in the extreme, having been found satisfactory in its present form for over ten years, each edition requiring only changes as evidenced by additional foods discovered as causative allergens, or by the repetitive listing of foods as known by their locally different names in one or more groups. Some species of fish differ by name as they are available in different geographical localities. Also, bran, for instance, is so defined because patients do not always know that it is derived from wheat. Patients do not always know that raisins are derived from grapes or prunes from plums. Synonymic terms are therefore given.

The instructions are simple. The patient places "0" before the foods he never eats. This information is extremely useful when making up per-

sonal or nonallergenic diets. The patient is forced to re-read the list, to list the foods he eats very rarely. As he goes down the list for the third time, familiarizing himself with it more and more, he double-checks those foods eaten on holidays or festivals, and then lastly, triple-checks the foods he eats daily. He underlines those which are known to cause difficulty, and encircles those he suspects as causing symptoms. The first page includes the more important foods, namely, meats, cereal grains, spices, nuts, and miscellaneous foods, which form a large part of the daily diet. The second page lists the vegetables, the fish, and the fruits. For reasons of simplicity, all aquatic sources of food are listed as fish.

The third questionnaire is not only the simplest but the most useful of the series. This includes the questions the physician or social service worker usually asks when he goes to a patient's home. These are the questions to which the patient rarely has the answers while at the physician's office. He can, at his leisure, furnish this information in detail.

The first page obviously introduces him to questions regarding his home, its type, its location as regards outside allergens, and its age, and the presence of environmental nonallergenic irritants, as well as dusts and molds. The second page informs the physician regarding the heating system, the types of materials available as stored, as well as the cleaning method and insecticides used. The third page is more specific and tells the physician what the bathroom and kitchen contain. The questionnaire tells us what is in the bedrooms and what hobbies are followed and in what part of the house. The question concerning stuffed trophies cannot be omitted, and the question as to how often they are cleaned is usually answered as "never."

The fourth page continues delving, still more deeply, into the patient's home environment. As is obvious, it requests information regarding hangings, rugs, and floor coverings, as well as nonspecific irritating fumes and odors. The last questions involve what may be brought into the home by the occupation of its members, and the final two are for children who may be at school part or all of the time. Again, as with each questionnaire, the patient is given scope to comment regarding any question which may be omitted. He is given room also to air his own suspicions.

It should be noted that all of the questionnaires have been copyrighted. This has been done only to prevent their use commercially. Any physician who desires to use them in their present form may do so, the only requirement being a letter to the author requesting permission. If any physician wishes to change or amend the questionnaire for his personal practice, he is to feel free to do so. The author will be grateful for any suggestions of improvement so that changes can be incorporated in future editions. For any member of the College who would like to have a supply sent him, the questionnaires are available without the titular heading for trial in actual practice. They are also available in quantities at cost from the Research Foundation.

DIAGNOSIS OF ALLERGIC CONDITIONS—BROWN

Questionnaire

FOR PATIENTS WITH RESPIRATORY SYSTEM ALLERGY AND SOME RELATED CONDITIONS

NAME: .....ADDRESS: .....

AGE: ..... OCCUPATION: ..... DATE: .....

Please underline or encircle the correct answers to the questions listed as they apply to you (or to your child), writing in the answer "Yes" or "No" when necessary. When the question does not refer to any present medical condition, please place a cross (X) either before or after it. If there are some facts, (however unimportant they may seem) concerning which no question has been asked, it should be written in at the end of the questionnaire. If you have any questions please make note of them so that they can be discussed at the visit held when the diagnostic studies have been completed.

1. Do you suffer from headaches? (Please encircle) ..... Yes? No?
2. If present, which part(s) of the head are affected? (Please underline) Forehead? Top? Sides? Back?
3. Do you know when a headache is coming on by change in vision? Spots? Lines? Colors? Dimness?
4. Are your headaches accompanied by: Nausea? Vomiting? Flatulence?
5. Are your headaches accompanied by stiffness or tenderness of the muscles of the neck? ..... Yes? No?
6. Do your headaches occur, as well, with colds? ..... Yes? No?
7. Are they worse in the morning? ..... Yes? No?
8. Do your headaches clear when your nose runs? ..... Yes? No?
9. Do you have frequent nasal blockage? ..... Yes? No?
10. Have you ever had a nose and throat examination? ..... Yes? No?
    When? ..... Where? .....
    By whom? .....
    Results (if known)? .....
11. Have you ever had a sinus X-ray? ..... Yes? No?
    When? ..... Where? .....
    By whom? .....
    Any abnormality present? .....
    What (if known)? .....
12. Have you ever been told that you have: Sinusitis? Polyps? Deviated Septum?
13. Do you sneeze? Rarely? Often? Continuously? In Attacks?
14. Is your sneezing seasonal? Spring? Summer? Fall? Winter?
15. Do you sneeze more in any special place? (Please underline) At home? At work? At school? At church? In crowds? At the mountains? At the seashore? In trains? On automobile trips? In museums? Libraries? Flower shows? Sport shows? County fairs? At the circus? Department stores? Any other place not listed? .....
16. If you sneeze more at home, is it worse in any one room? ..... Yes? No?
    Bedroom? Living room? Kitchen? Dining room? Bathroom? Cellar? Attic? Playroom? Barn? Kennels? Chicken coop? Any other place not listed? .....
17. Do you have frequent colds? ..... One or two each year? ..... Three or four? ..... More? .....
18. Do you sneeze only with colds? ..... Yes? No?
19. Do you seem to catch colds easily? ..... Yes? No?
20. When you have a cold do others seem to catch it from you? ..... Yes? No?
21. Does handling any one thing(s) make you sneeze? Please describe. .....
22. Is your sneezing worse with exposure to frying foods? Kerosene stoves? Fresh paint? Perfumes? Barber shops or beauty parlors? Tobacco smoke? Wood smoke? House dust? Hay? Grain? Animals (which)? .....
    Cold air? Warm air? Steam?

23. Is your sneezing worse with eating of any food(s)? Which? .....
.....
24. Is your sneezing worse with the taking of any medicines? Which?
.....
25. When you sneeze does your nose run? ..... Yes? No?
26. If present, is the discharge thin?.....
Watery? Thick?
27. How long does the discharge usually last? Several minutes?.....
Several hours?..... All day?..... Until
you take medicine (which)? .....
28. When you sneeze do you have itching of the eyes? ..... Roof
of the mouth? ..... Inside ears? .....
Throat? .....
29. Do you sometimes have mucus at the back of your throat?..... Yes? No?
30. Have you ever been treated for hay fever? ..... Yes? No?
When? ..... Where? .....
By whom? .....
For how long? .....
With what (if known)? .....
31. Do you have "sore throats"? .....
Frequently? ..... Rarely? .....
32. Do they occur with colds? ..... fever? .....
chills? ..... tonsillitis? .....
33. Have your tonsils been removed? ..... Yes? No?
When? ..... Where? .....
By Whom? .....
34. Have you ever had streptococcal sore throat?.....
Scarlet fever? ..... Measles? .....
Whooping cough? ..... Influenza? .....
When (for each): .....
.....
.....
35. Do you smoke? ..... Yes? No?
Cigarettes? ..... Cigars? ..... Pipe?.....
How many (or much) daily? .....
36. Have you had any recent hoarseness? ..... Yes? No?
With colds only? ..... Without colds? .....
Both? .....
37. Do you have indigestion? ..... Yes? No?
With any one food(s)? ..... With all
foods? ..... Independently of food? .....
38. Do you cough? ..... Yes? No?
39. Is your cough present only with colds?..... Yes? No?
40. Is your cough associated with fever? .....
Tonsillitis? ..... Sinusitis? ..... Laryngitis? .....
Pharyngitis? ..... Bronchitis? .....
Pneumonia? ..... Pleurisy? .....
41. Do you raise any mucus? .....
Very little? ..... Much? .....
42. If you do, does it relieve the cough? ..... Yes? No?
43. What sort of mucus do you raise, if any?
White, frothy? ..... Thick, lumpy? .....
Thin, watery? ..... Rusty? .....Blood-
tinged (red)? ..... Yellow-green? .....
Pus? .....
44. Is your cough worse in winter? .....
Spring? ..... Summer? ..... Fall? .....
Not seasonal? .....
45. Have you ever had influenza? .....
Bronchitis? ..... Pleurisy? .....
Pneumonia? ..... Tuberculosis? .....
Rheumatic heart disease? ..... When
(for each, if any)? .....
.....
46. Have you ever breathed a "foreign body" into your lungs? .....
What? ..... When? .....

47. Is your cough (if present) associated with lack of breath? .....
Before? ..... After? ..... With exertion? .....
Please describe. .....
.....
.....

48. Have you recently gained weight? .....
Lost weight? ..... How much? .....

49. Do you cough following exposure to fumes? .....
Tobacco smoke? ..... Wood smoke? .....
Kerosene stoves or heaters? ..... Frying foods? ..... Cooking smells? ..... Fresh paint? ..... House dust? ..... Perfumes? .....
Barber shops or beauty shops? .....
Hay? ..... Grain? ..... Animals (which)? .....
Cold air? ..... Warm air? ..... Steam? .....

50. Does the eating of any specific food make you cough? .....
Which? .....

51. Do you cough when you are tired? .....
Nervous? ..... Emotionally disturbed? .....

52. Is your cough continuous? .....
In attacks? .....

53. Have you ever "blacked out" while coughing? ..... Yes? No?

54. Does your cough appear at bedtime? ..... Yes? No?

55. Does your cough ever awaken you at night? ..... Yes? No?
Once or twice? ..... Three or four times? ..... More often? .....

56. Do you cough when waking in the morning? .....
In bed? ..... On getting out of bed? .....
While dressing? ..... In bathroom? .....
At breakfast? .....

57. Is your cough worse, if when resting or sleeping, you lie on one side of the body.....
Which side? .....
Otherwise? .....

58. What (if known) have you taken for relief? .....
.....

59. Is the cough (if present) associated with a wheeze? ..... Yes? No?

60. Do you cough and **then** wheeze? ..... Yes? No?

61. Is the wheezing (if present) relieved when you cough up some mucus? ..... Yes? No?

62. Do you wheeze only with colds or bronchitis? ..... Yes? No?

63. Is your wheezing worse with any season? ..... Yes? No?
Winter? ..... Spring? ..... Summer? .....
Fall? .....

64. Is the wheezing worse in any special place? (Please underline) At home? At work? At school? At church? In crowds? At the mountains? At the seashore? In trains? On automobile trips? In museums? Libraries? Flower shows? Sport shows? County fair? Circus? On picnics? Theatres? Department stores? Any place not listed? Please describe. .....
.....
.....

65. If the wheezing is worse at home does it occur in any one room(s)? Bedroom? Living room? Kitchen? Dining room? Bathroom? Cellar? Attic? Play room? Barn? Kennels? Chicken coop? Any place not listed (Please describe).....
.....
.....

66. If it occurs at work, please describe occupation: .....

67. Please list the occupations of all members of your family: .....
.....
.....
.....
.....
.....

68. Have you ever gone on a trip for relief of your wheezing? .....
When? .....
Where? .....
What result? .....
69. Is your wheezing continuous? ..... In attacks? .....
Continuous and worse in spasms? .....
70. How long does an average attack last?.....
Minutes? ..... Several hours? .....
Several days? ..... Until you take medicine? .....
71. What medicine (if any and known) relieves you? .....
72. How long have you wheezed altogether (however little)? .....
73. How long has your longest period of freedom lasted? .....
When? .....
74. Is your wheezing worse with fatigue? .....
Emotional upsets? ..... Laughter? .....
Nervousness? .....
75. Was your wheezing preceded by hay fever? ..... Yes? No?
76. Is your wheezing worse on clear sunny days? .....
In damp, humid weather? .....
77. Have you ever had skin tests? .....
When? ..... Where? .....
By whom? .....
What results (if known)? .....
78. Have you ever had injection treatments? ..... Yes? No?
When? .....
Where? .....
By whom? ..... For how
long? ..... With what
(if known)? .....
.....
79. Have you ever had a chest X-ray? .....
When? ..... Where? .....
By whom? .....
Results (if known)? .....
.....
80. Have you ever had a pain in the chest? ..... Yes? No?
81. Can you describe its location? .....
82. When is it present? Any time? .....
With coughing? ..... With effort? .....
At night only? ..... With pleurisy? .....
With bronchitis? ..... Other conditions? .....
.....
83. What is it like? .....
.....
.....
84. How long does it last? ..... Minutes? .....
Hours? ..... Days? .....
85. What do you do for relief? .....
.....
.....
86. Have you ever had any swelling of the ankles? ..... Yes? No?
87. If present, is the swelling worse at the end of the day? .....
In hot weather? ..... When you have been on your
feet for an unusually long period of time? .....
88. Is it less after resting or sleeping? ..... Yes? No?
89. Have you ever had an electrocardiogram? .....
When? .....
Where? .....
By whom? .....
Results (if known)? .....
.....
90. Have you ever had a complete physical examination? .....
When? .....
Where? .....
By whom? .....
Anything abnormal discovered? Please describe, if known)?.....
.....

91. Have you ever been in a hospital or sanatorium? .....
When? .....
Where? .....
For what condition(s)? .....
For how long? .....
92. Have you ever had eczema? ..... Yes? No?
93. At what age did it appear? .....
94. If not still present, at what age did it clear? .....
95. What parts of the body were affected? .....
Face? ..... Neck? ..... Front of elbows? ..... Behind knees? .....
All over? .....
96. Did you have treatment for it? ..... Yes? No?
When? .....
Where? .....
By whom? .....
Results? .....
97. Do any foods or drugs cause your skin to "break out?" .....
Which? .....
In what way? .....
98. Did your father ever have eczema? .....
Hay fever? ..... Sinusitis? .....
Bronchitis? ..... Bronchial asthma? .....
Colitis? ..... Sick headaches? .....
99. Did your mother ever have eczema? .....
Hay fever? ..... Bronchits? .....
Sinusitis? ..... Bronchial Asthma? .....
Colitis? ..... Sick headaches? .....
100. Has any other blood relative had any of the conditions listed?..... Yes? No?
Who? Which?
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....

FOOD CHECK LIST

The following list is used to discover what foods, if any, may be the cause of your present symptoms. In some patients the cause may not be difficult to discover by the patient himself if his symptoms are due to a specific food which he eats rarely. On the other hand, when symptoms occur very frequently and are caused by a food eaten often, the relationship is not always apparent.

The foods are listed in groups. The list should be examined carefully and a "0" placed beside the foods which are never eaten. The list must then be examined for the foods which are eaten very rarely, or only when they are in season and a "X" is placed to the right of these foods. This having been done, the list should be examined again for the foods eaten once or twice a week, as on Fridays, week-ends, special holidays, picnics or trips. Besides these foods two marks should be placed. For the fourth reading three marks should be placed beside the foods which are eaten every day, once or twice daily, or at least as often as once in two days. If any food has been omitted, it should be noted at the bottom of the sheet under the heading "Miscellaneous," with its proper markings. If there is any food which is usually purchased partially or wholly cooked, and whose composition is not certain, that food should be listed with its appropriate marking. If any food is known, the eating of which causes immediate symptoms, it should be underlined. If any food is suspected as causing any difficulty, it should be encircled.

Meats

Bacon
Beef
Calves' liver
Elk
Deer
Goat
Ham
Horse
Kid
Lamb
Moose
Mutton
Pork
Rabbit
Veal

Fowl

Chicken
Duck
Goose
Guinea Hen
Partridge
Pheasant
Quail
Squab
Turkey

Cereals

Arrow Root
Barley
Barley Malt
Bran
Buckwheat
Corn
Oats
Rice
Rye
Sago
Soya Bean
Tapioca
Wheat
Yeast

Condiments

Allspice
Anise
Basil
Bay Leaves
Capers
Caraway
Cayenne Pepper
Celery Seed
Cinnamon
Citron
Cloves
Curry
Dill
Garlic
Ginger
Hops
Horse-radish
Marjoram
Mace
Mint
Mustard
Nutmeg
Oregano
Paprika
Pepper
Peppermint
Poppyseed
Rosemary
Saffron
Sage
Savory
Sesame seeds
Turmeric
Tarragon
Thyme
Vanilla

Beverages

Beer
Coca-Cola
Cocoa
Coffee
Chocolate
Liqueurs
Tea
Whiskey
Wine
Others?

Nuts

Almond
Brazil
Butternut
Cashew Nut
Chestnut
Coconut
Hazelnut (Filbert)
Hickory Nut
Peanut
Pecan
Pignolia
Pistachio
Walnut

Miscellaneous

Cheese (? type)
Eggs
Honey
Milk:
  Goat's
  Cow's

Vegetables	Fish	Fruits
Artichoke	Abalone	Apple
Asparagus	Anchovy	Apricot
Avocado	Barracuda	Banana
Beans	Bass	Blackberry
Beets	Bloater	Blueberry
Broccoli	Bluefish	Boysenberry
Brussels Sprouts	Buffalo	Cantaloupe
Cabbage	Butterfish	Casaba
Carrots	Carp	Cherry
Cauliflower	Catfish	Cranberry
Celery	Clam	Currant
Chicory	Codfish	Date
Chili Pepper	Crab	Elderberry
Chives	Crawfish	Fig
Corn	Eel	Gooseberry
Cucumber	Flounder	Grape
Dandelion	Frog	Grapefruit
Eggplant	Haddock	Honey Dew Melon
Endive	Halibut	Huckleberry
Garlic	Herring	Juniper Berry
Horseradish	Kingfish	Lemon
Kale	Kipper	Lime
Kohlrabi	Lobster	Loganberry
Leek	Mackerel	Mango
Lentil	Mussel	Mulberry
Lettuce	Mullet	Nectarine
Lima Beans	Oyster	Orange
Mushrooms	Perch	Papaya
Okra (gumbo)	Pickerel	Peach
Olive	Pike	Pear
Onions	Pompano	Persimmon
Oysterplant	Porgy	Pineapple
Parsley	Quahaug	Plum
Parsnip	Red snapper	Pomegranate
Peas	Salmon	Prunes
Peppers	Sardine	Quince
Pimento	Scallop	Raisin
Pumpkin	Scrod	Raspberry
Radish	Shad	Strawberry
Rhubarb	Shrimp	Tangerine
Rutabaga	Smelt	Watermelon
Spinach	Snail	Youngberry
String Beans	Sole	
Summer Squash	Squid	
Sweet Potato	Sturgeon	
Swiss Chard	Swordfish	
Tomato	Terrapin	
Turnip	Trout	
Watercress	Tuna	
Winter Squash	Turtle	
White Potato	Whitefish	
Yam	Weakfish	
	Whiting	

Questionnaire

ENVIRONMENTAL SURVEY FOR PATIENTS WITH SUSPECTED INHALANT SENSITIVITIES

NAME: ..... ADDRESS: .....

AGE: ..... OCCUPATION: ..... DATE: .....

In order to discover the cause of the patient's allergic symptoms, it is necessary for the physician to have detailed information of the patient's home, school, and occupational environment. The following questions should be given careful study and checked when applicable to the patient being studied.

1. Is the house in which you live situated in: the city? the country? the suburbs?
2. Is it: one-family? two-family? three-family? apartment house? other?
   PLEASE DESCRIBE
3. Do you live near any: factory? railroad? lake? swampy area? farms? poultry yard? barn? other?
   PLEASE DESCRIBE
4. How old is your house? Has it recently been: altered? painted? varnished? shellacked? plastered? shingled? renovated? other?
   PLEASE DESCRIBE
5. Are there any damp places in: attic? outdoor porch? basement? kitchen? other?
   PLEASE DESCRIBE
6. How is it heated? fuel oil? gas? coal? coke? wood? electricity? kitchen oil? oil range? coal range? other?
   PLEASE DESCRIBE
7. If wood is used for fireplaces, stoves or furnaces, is it stored: outside? in the kitchen? in the room in which used? in the cellar? in a bin?
   PLEASE DESCRIBE
8. Does the heating system use: ducts? radiators? fans? blowers? filters? other?
   PLEASE DESCRIBE
9. What plants are usually kept in the house? cut plants (if ever)? growing plants? any window boxes?
   PLEASE DESCRIBE
10. If the cellar is used for storage, what does it contain: summer furniture? other furniture? bulbs for planting? books? paper? clothes closets? toys? winter vegetables (in bins)? other?
    PLEASE DESCRIBE
11. What are the cleaning methods used: broom and mop? carpet sweeper? vacuum cleaner (type)? other?
    PLEASE DESCRIBE
12. What insecticides or moth-killing preparations are used: in the house? generally? summer? winter? regularly? in closets only? in cellar only? where is the material stored?
    PLEASE DESCRIBE
13. Please list by name all preparations stored in bathroom, including medicine cabinet (quantity not necessary):

14. Please list by name complete contents of kitchen shelves, including all boxed (BUT NOT CANNED) foods (quantity not necessary):

15. Please list number of: beds, mattresses, pillows, daybeds, sofas, couches. check stuffings present:

Down filled?	Feather filled?	Cotton filled?
Horse hair?	Rabbit hair?	Kapok?
Cow hair?	Hog hair?	Mohair (goat)?
Glass fibre?	Rubber?	Felt (type)?
Mixtures?	Allergia?	Other?

PLEASE DESCRIBE

16. Are allergen-proof covers used: on pillows? all pillows? on mattresses? all mattresses? on stuffed furniture? all stuffed furniture? on inner springs? other?

PLEASE DESCRIBE

17. What types of bedspreads are present?

PLEASE DESCRIBE

18. What hobbies are followed by any or all members of the household: in living room? kitchen? bedroom? playroom? attic? basement? special room? barn?

PLEASE DESCRIBE

19. What pets (bird or animal) are kept: indoors? outdoors? in barn? close to house?

PLEASE DESCRIBE

20. Are any stuffed trophies (bird or animal) in the house? where are they placed? stored? how often cleaned?

PLEASE DESCRIBE

21. What hangings, if any, are present? silk rugs? Indian rugs? velvet portieres? tapestries? velour? plush? other?

PLEASE DESCRIBE

22. Please list all floor coverings for all rooms: linoleum? wool rugs? cotton rugs? underlays, rug pads? of each, how many? other?

PLEASE DESCRIBE

23. Please list any items of which there may be a considerable collection in your home, as: china? bric-a-brac? books? antique furniture? other?

PLEASE DESCRIBE

24. Are there any fumes or smells continuously or frequently present, as from: furnace? kitchen stove? gas heater? auxiliary oil (range)? heater? refrigerator? from hobbies (glue, photography)? cooking? preserving? sachets or perfumes? air purifiers? mildewed places? other?

PLEASE DESCRIBE

25. List the occupations of each member of the household:

26. If the patient is at school does he return home at night? return for week-ends? return for vacations?

27. If the patient stays at school does he have his own room? Does he stay in a dormitory? Does he share a room?

28. Aditional comments regarding any environmental place or substance suspected of causing symptoms or making them worse should be noted at this point.

TOXIC CUTANEOUS MANIFESTATIONS OF PARA-AMINOBENZOIC ACID DERIVATIVES

GLENN J. GREENWOOD, D.D.S., M.D., F.A.C.A.
Los Angeles, California

IN THE current treatment of infections, multiple chemotherapeutic remedies thought to be synergistic may excite antagonistic responses. When allergic cutaneous manifestations occur, it is often difficult to determine what the offending antigen may be.

Experiences concerning antibiotics and para-aminobenzoic acid or its derivatives, coupled with the use of sulfonamides, have been reported.[2,6,7,9,10,12] Now with the advent of procaine for intravenous therapy[3,1] (it has long been used parenterally), we can well look for more bizarre toxic responses in an already complicated therapeutic regime. A case in point is herein presented.

On March 3, 1949, Mr. E. H., a plethoric individual of forty, weighing 148 pounds, presented himself for treatment of a subacute pruritus. The general intense involvement was particularly annoying in his extremities. Ten to twelve years previously an undetermined sulfonamide had been prescribed for an acute pneumonitis. There resulted a severe headache accompanied by general malaise, but with no toxic skin reactions.

In early November, 1948, he had what was thought to be a virus pneumonia, for which he was given two injections of procaine penicillin with excellent effect. Approximately seven to ten days later his body was cerisely patched, especially upon his feet, where an old epidermophytosis persisted. Apparently, epinephrine subcutaneously and an antihistaminic drug by mouth, with a topical ointment, gave him relief. However, he had two relapses in the following weeks. After one of these he had three infected teeth extracted under procaine block anesthesia. There followed an increased reappearance of symptoms with intense itching accompanied by "hives" upon his hands, wrists, feet, legs and left buttock. Treatment apparently gave little relief. He admitted to drinking much alcohol at that time.

So far as he recalls, no allergic symptoms occurred following his childhood immunizations or illnesses. He admitted to chronic alcoholism and much smoking as an adult.

His father had many perennial attacks of rhinitis. His mother had had bronchial asthma. Further history was not pertinent to his present illness.

Physical examination revealed the intense general erythema, partially obscured ventrally under a heavy hairy growth upon the extremities. There was moderate diffuse edema of both upper and lower extremities. Large hemorrhagic tinged bullae were present over the dorsum of his hands and wrists, but greatest upon the left extremity, where their confluency seemed to follow a linear arrangement overlying a moderately severe lymphangitis. Both legs were similarly involved. No lymphangitis was present. Regional nodes were not noticeably enlarged. The remainder of the physical examination was negative.

The laboratory findings showed both sugar and acetone once, only upon the initial analysis. The hemoglobin was 17.4 gm per cent, red blood cells 5,200,000;

Presented at the Sixth Annual Meeting of the American College of Allergists, January 15-18, 1950, St. Louis, Missouri.

From the Medical School of the University of California at Los Angeles.

white blood cells numbered 9850, of which 60 per cent were neutrophiles, only two eosinophiles showing. The sedimentation rate was within normal limits.

Therapeutically an antipruritic regime was started. Procaine, 0.25 per cent intravenously, was ill-advisedly started but quickly stopped when it elicited a marked increase of all symptoms and signs. In addition there was precordial pain. The pruritus was extreme. The erythema became more dusky, with some weeping of the bullae. The temperature rose to 99.8°. The respiratory tract remained clear.

Intramuscular ephinephrine, 0.5 cc in oil, and 50 cc of 50 per cent glucose intravenously were given. Demerol, 200 mg intramuscularly, and topical hot magnesium sulphate packs were used. Because Pyribenzamine unguentum had previously provoked a pruritus, antihistamines were not risked.

Recovery was uneventful. A cardiologist's consultation proved no abnormality to be present. Some months later a 2 per cent procaine sensitization test intradermally elicited a vesicular reaction, while a sulfanilamide patch test was negative. Penicillin, epidermally and intradermally, gave no response.

Para-aminobenzoic acid is one of the B complex factors. Derivatives of it are sulfanilamide and procaine. From procaine: pontocain, larocain, butyn, benzocain, monocain, and tutocain are formed.[11] The base of each of these compounds is aminobenzene (analine).[9] Thus, there is here a rationale for a sensitization reaction from subsequent use of any one of these compounds in patients initially allergic to this base.

With penicillin, it is known that where cutaneous sensitization to a mold exists, other generic molds excite antigenic responses. Also where eczematoid lesions have previously existed, penicillin in 50 per cent of the cases causes dermatosis.[4,5,11]

The use of procaine in modern therapy is noticeably increasing, particularly intravenously.[1,3] Its use when coupled with penicillin is twofold: it allays pain and it has an antihistaminic action. Here it may further potentiate complicating sensitizations. As Peck has indicated, a weak linkage may exist between procaine and penicillin.[8]

In conclusion, it would seem discreet to exercise considerable caution in caring for an increasingly allergic population. Even better, if possible one should foster a natural defensive mechanism to correct itself, rather than hasten to utilize new and possibly not well tried foreign sensitizing antigenic therapy. Likewise a better grounding in organic chemistry would seem to be one of this specialty's responsibilities in undergraduate medical teaching.

In summary, a case of multiple procaine sensitivity is reported. The compounding and prescribing of inadequately tried chemotherapeutic remedies, that may potentiate antigenic responses, is described.

REFERENCES

1. Bittrich, N. M., and Powers, W. F.: Intravenous procaine in thoracic surgery. Anesth. & Analg., 27:181, (July-Aug.) 1948.
2. Finney, J. O.: Severe dermatitis medicamentosa following the administration of sulfanilamide. J.A.M.A., 109:1982, (Dec.) 1937. Quoted by Rogers, E. B.[9]

(Continued on Page 94)

BENADRYL—ITS USES IN THE NARCOTIC WITHDRAWAL SYNDROME AND IN OTHER CONDITIONS

MAURICE VAISBERG, M.D.
Miami Beach, Florida

THE sedative action of Benadryl in some persons is well known. Advantage of this property can be taken in the treatment of the withdrawal syndrome of drug addiction both to shorten the duration of treatment and to lessen the amount of drug required. It is an accepted and recognized axiom that the treatment of drug addition on an ambulant basis is doomed to failure except in the extremely rare case of an intelligent and completely co-operative patient, and that to achieve any degree of success, institutionalization is required.

The present studies concern two patients who were "hospitalized" at home under the constant supervision of two competent graduate nurses during the entire period of treatment. The third patient was an exceptional, intelligent person who was treated on an ambulant basis. Other studies were made on persons requiring narcotics for relief of pain and asthma. Injectable Benadryl and Benadryl solution were also used in other conditions which will be described.

The Benadryl used in these studies was the stock Steri-Vial Benadryl Hydrochloride (Parke, Davis & Company), each cc containing 10 mg.

Case 1.—A thirty-five-year-old woman who had been addicted many years through association agreed to have complete supervision at home with nurses. Her daily dose had been in the neighborhood of two to three grains of morphine sulfate. In twenty-four hours she was stabilized on morphine sulfate gr ¼ every four hours, day and night. She was then switched to Dolophine 10 mg every four hours, day and night. All injections were given with a 5 cc syringe and the volume adjusted to 5 cc with saline. She was allowed to see the volume in the syringe for psychological reasons.

The schedule followed was:

	Dolophine	*Benadryl (10 mg per cc)*	*Saline q.s.*
2nd day	10 mg	1 cc	
3rd day	7 mg	2 cc	
4th day	4 mg	2½ cc	
5th day	2 mg	3 cc	
6th day	none	3 cc	
7th day	none	3 cc	
8th day	none	2½ cc	
9th day	none	2 cc	
10th day	none	1 cc	

She did very well, had a voracious appetite, and experienced a minimum of withdrawal symptoms. For sleep, two capsules (gr 3) seconal were given at night until the sixth day, when 100 mg Benadryl was substituted in the following manner: The seconal capsule was emptied and a 50 mg capsule of Benadryl inserted into

Doctor Vaisberg is an Associate Fellow of The American College of Allergists.
Material supplied by the Department of Therapeutic Development, Parke, Davis & Co.

the empty red capsule. This was given for a total of three weeks nightly. In addition, during the period of injections, 50 mg of Benadryl was given orally, three times daily.

Case 2.—A fifty-year-old woman who had had severe asthma of long duration and had thus acquired a medical addiction to Demerol to the extent that she required from 30 cc to 60 cc Demerol per day for relief of the asthma. After a successful bronchoscopy, her asthma disappeared but she developed a severe withdrawal syndrome. She was stabilized on 100 mg Demerol (2 cc) for the first day and then switched to Dolophine every four hours for the second day. A schedule similar to Case 1 was used, and she did very well in a period of seven days of injections. Benadryl was given orally in addition, as in Case 1. Her nutritive status was enhanced by the administration of Lactenz (a protein hydrolysate) in doses of 8 tablespoons per day in milk.

Case 3.—This was an ambulant, intelligent man of forty-eight who had acquired a "habit" after indulging in alcohol. He had been given morphine elsewhere for the "hangover." The patient continued to drink, and in this vicious cycle he had built himself up to 1½ grains of morphine per day taken once a day at one dose in a single twenty-four-hour period. This had occurred each year in the springtime for the past three years.

The following schedule of treatment was developed:

	Morphine Sulfate (gr) Only One Injection per Day	*Dolophine*	*Benadryl (10 mg per cc)*	*Saline q.s.*
1st day	1½	none	1 cc	
2nd day	1	none	2 cc	
3rd day	¾	10 mg	2½ cc	
4th day	none	10 mg	3 cc	
5th day	none	7 mg	3 cc	
6th day	none	4 mg	3 cc	
7th day	none	2 mg	3 cc	
8th day	none	none	3 cc	

He was given 50 mg Benadryl orally three times daily and the following supportative medication:

Six capsules of vitamins each day, each capsule containing thiamine 100 mg, ascorbic acid 150 mg, nicotinamide 200 mg, and riboflavin 50 mg.

Twelve capsules of Methischol, each capsule containing choline dihydrogen citrate .277 gm, dl-methionine .112 gm, and inositol .083 gm.

Six tablespoons of Ledinac (protein hydrolysate) in milk daily.

Methischol has a lipotropic action and appears to lessen the "craving" for alcohol and to a lesser extent the "desire" for narcotics.

In several cases of migraine the slow intravenous injection of from 10 to 30 mg of Benadryl produced immediate relief. This could not be duplicated in some other cases.

In some cases of allergic rhinitis there has been relief of stuffiness by the use of Benadryl solution (10 mg per cc) used as a spray. Quite a number of patients with asthma were relieved by using Benadryl solution (10 mg per cc) as an aerosol. Relief was more marked when used at the onset of an attack. Utilized this way, Benadryl seems to have an additional effect on the bronchial mucosa. It not only controls an early

attack through its antihistaminic action, but also exerts an anesthetic effect on the mucosa, thus relieving "reflex" spasm due to irritating secretions.

There are certain injectable medications which produce a local itching and wheal formation at the site of injection—notably codeine and morphine. The addition of 1 cc (10 mg) of injectable Benadryl minimizes these undesirable local reactions and the generalized itching which occurs in some persons after morphine injections.

Injectable Benadryl seems to have an additive and potentiating action when used along with narcotics for the relief of actual pain and with Demerol for the relief of asthma. In a series of patients who had recurring episodes of pain from kidney stones, cholelithiasis, and intestinal upsets, and in whom the usual dose for relief was established at from ¼ to ½ grain of morphine, this dose could be cut as much as 25 to 50 per cent by the addition of from 10 to 20 mg (1 to 2 cc) Benadryl in the injection. Two patients who required 100 mg (2 cc) Demerol for regular relief of asthmatic attacks could obtain the same degree of help with 50 mg when 20 mg (2 cc) Benadryl was added to the injection. No attempt was made to use Benadryl in relief of the emergency and severe pain caused by coronary occlusion and spasm because of the immediate severity of the condition.

SUMMARY

Injectable Benadryl is a valuable adjunct in the treatment of the narcotic withdrawal syndrome in reducing the time required and the amount of drug needed. In addition, 50 mg oral Benadryl is of further aid. Injectable Benadryl has an additive and potentiating action when used with narcotics and helps reduce the dose required for relief of pain. The amount of Demerol can be reduced by as much as 50 per cent when 20 mg of Benadryl is used along with it for the relief of asthma.

Injectable Benadryl is of value in some cases of migraine when given intravenously in doses of from 10 to 30 mg.

Benadryl solution spray is an excellent nasal mucosal constrictor and helps abort some attacks of asthma, especially when the latter has a large "reflex" element.

Injectable Benadryl can be used along with wheal-producing drugs to reduce local and generalized itching and discomfort.

However, it must be remembered that the above-mentioned effects are not observed in every patient, but tend to occur in that large group in which some sedation from Benadryl is produced.

The author wishes to thank the Department of Therapeutic Development, Parke, Davis & Company, for a most generous supply of injectable Benadryl used in this work and for its helpful co-operation.

605 Lincoln Road

INJECTIONS OF MASSIVE DOSES OF POLLEN EXTRACT AT THREE-WEEK INTERVALS AND THEIR EFFECT ON SKIN-TEST SENSITIVITY

HENRY I. SHAHON, M.D., F.A.C.P., F.A.C.A., A. HENRY LAPPIN, M.D., F.A.C.A., VICTOR AGRANAT, M.D., F.A.C.A., IRVING KAMBERG, D.P.H., M.D., and FRED A. PARISH, M.D., F.A.C.A.

Boston, Massachusetts

THE perennial method of treatment of hay fever was first adopted by Brown[2] and later by Van der Veer, Cooke, and Spain.[29] Figley[10] reported that of a group of 125 patients treated perennially, there were ten "cured" cases. All of these patients presented negative skin reactions two years after treatment had been discontinued. Vaughan,[30] Unger,[27] Sutherland,[25] and Feinberg[9] all stressed the value of this type of therapy. Gay[11] stated that when hay fever patients received treatments perennially, they experienced fewer symptoms than when treated preseasonally. Colmes[6] favored this form of treatment also, but stated that his hay fever patients had more frequent constitutional reactions.

Peshkin[20] discovered that hay fever patients had more frequent general reactions when treated perennially than when treated preseasonally. Sweetster[26] stated that the failures obtained in the treatment of hay fever were usually due to insufficient treatment and to the improper understanding of the mechanism of desensitization. Van der Veer[28] stated that the choice between the perennial and preseasonal form of treatment of hay fever depended chiefly on the indications in each particular case. Hinnant and Evans[12] also favored the perennial treatment. Clarke and Leopold[4] felt that the perennial treatment is much less satisfactory than prophylactic treatment. Spain and Fuchs,[24] in a comparative study of 692 hay fever patients treated preseasonally and 258 patients treated perennially, discovered that of those treated preseasonally, 508 patients (73.4 per cent) did well, and 184 patients (26.6 per cent) did poorly. Of the 258 patients treated perennially, 243 (94.2 per cent) did well, and fifteen (5.8 per cent) did poorly. Shahon[23] obtained similar results with the perennial type of treatment.

Cooke,[8] in regard to clinical sensitiveness, stated, "we understand little of the basic facts, and there are many problems still to be solved." He is of the opinion that the positive skin test itself is not a criterion of clinical sensitiveness, and that the results of treatment leave much to be desired. Cohen[5] stated that there is some question as to whether the thermostable antibodies can completely explain the relief in treated hay fever patients, but as yet it is the only mechanism based on immunological principles. Rockwell[22] maintains that the maximum tolerated doses in hay fever patients usually give the best results. Brown[3] states that "the degree of hypersensitization may lie on the proportional increase of what appears

Presented at the Sixth Annual Meeting of the American College of Allergists, January 15-18, 1950, St. Louis, Missouri.

to be a double type of response to a single botanical, but actually an immunologically multiple, biochemical stimulus."

Rackemann[21] maintained that the level of the absolute tolerance in the treatment of hay fever appeared to be at a point more or less fixed for each patient. When that point can be recognized, the general or systemic reaction can be minimized, and in this way, the dose can be held below the level of tolerance. He also stated that there is no way of determining the level of absolute tolerance excepting by way of trial and error. In reference to the reduction in skin-test sensitivity, following perennial treatment, Lamson, Piness, and Miller,[14] Markow and Spain,[17,18] and Colmes and Rackemann[7] have all stated that massive doses of pollen therapy result in some reduction in skin-test sensitivity. Levin[15] noted that clinical relief occurred in some cases without much change in the clinical reaction, and that the greater the initial skin reaction, the greater the diminution of the skin reaction after treatment. Naterman[19] maintained that patients treated with extract of ragweed tannate showed a reduction in the skin sensitivity.

Immunological studies on pollenosis were done by Loveless.[16] Her studies on immunity recently disclosed the technique of the conjunctival test as a guide to clinical immunity in hay fever. She concluded that it revealed the threshold of reaction, and in this manner found that it was an important clinical guide to the amount of specific treatment required by the hay fever patient. Thus, a patient showing a threshold of 350 or better is more likely to have better clinical results than the one having 35 or less.

Johnson, Alexander, Alexander and Walker[13] demonstrated the presence of ragweed antigen in the sera of hay fever patients. They proposed to study the correlation between the amount of this circulating antigen, and the thermostable antibody, and reagins—also the relation of these values to the dosage of the pollen extract and the pollen count.

In the fall of 1950 a study was made of the ragweed hay fever patients treated perennially at the Boston Evening Clinic and Hospital. About 80 per cent of the patients were receiving injections of massive doses of ragweed extract, ranging from 2,500 to 10,000 protein nitrogen units (Cooke and Stull) at intervals of three weeks, instead of the usual four-week period.

Before any form of treatment was started, all patients were classified arbitrarily according to Classes AA, A, B, and C. That is, if a patient gave a marked reaction to 1 protein nitrogen unit, on intracutaneous testing, he was classified as Class AA; to 10 PN units, he was classified as Class A; to 100 PN units, as Class B; and to 500 PN units, as Class C. Only Class B and C patients were treated perennially, with injections administered every three weeks throughout the year, and every two weeks during the hay fever season. The schedule, as shown in Table I, was followed as closely as possible during the first year of treatment. However, in the second, third, and fourth years of treatment and thereafter,

TABLE I. PROPHYLACTIC TREATMENT, AVERAGE DOSAGE FOR VARIOUS CLASSES, GIVEN IN STULL-COOKE UNITS (PROTEIN NITROGEN)

	CLASS AA 1 Unit Marked 10 Units Marked Plus Units	CLASS A 10 Units Marked 100 Units Marked Plus Units	CLASS B 100 Units Marked 500 Units Marked Plus Units	CLASS C 100 Units Moderate 500 Units Marked Units
Test Day	0	0	0	0
Inj. 1	2	5	10	10
Inj. 2	5	10	20	20
Inj. 3	10	20	40	40
Inj. 4	20	30	70	70
Inj. 5	30	40	100	100
Inj. 6	40	60	200	200
Inj. 7	50*	80	300	400
Inj. 8	—	100	400	700
Inj. 9	—	150	600	1000
Inj. 10	—	200	800	1250
Inj. 11	—	300	1000	1500
Inj. 12	—	400	1250	1750
Inj. 13	—	500*	1500	2000
Inj. 14	—	—	1750	2250
Inj. 15	—	—	2000	2500
Inj. 16	—	—	2250	3000
Inj. 17	—	—	2500*	3500
Inj. 18	—	—	—	4000
Inj. 19	—	—	—	5000*

*This dose continued at 5 to 7 day intervals during the season.

TABLE II. THIRTY-SEVEN B PATIENTS

	Test Reaction on Admission to 500 Units	Top Dose First Year	Top Dose After First Year	Test Reaction After Three Years — 0 + 16 ++ 16 +++ 5	Degree of Improvement W 19 54% FW 14 35% B 4 11%
1	++++	2500 U.	3500 U.	+	FW
2	++++	2500 U.	4000 U.	+	FW
3	++++	2500 U.	5000 U.	++	W
4	++++	2500 U.	5000 U.	+	W
5	++++	2500 U.	4500 U.	++	W
6	++++	2500 U.	5000 U.	+	W
7	++++	2500 U.	5000 U.	++	W
8	++++	2500 U.	3500 U.	+++	FW
9	++++	2500 U.	4500 U.	++	B
10	++++	2500 U.	5000 U.	++	W
11	++++	2500 U.	3500 U.	+	FW
12	++++	2500 U.	5000 U.	++	W
13	++++	2500 U.	5000 U.	++	W
14	++++	2500 U.	3500 U.	++	FW
15	++++	2500 U.	5000 U.	++	W
16	++++	2500 U.	5000 U.	++	W
17	++++	2500 U.	3500 U.	++	FW
18	++++	2500 U.	5000 U.	+	W
19	++++	2500 U.	4000 U.	++	B
20	++++	2500 U.	5000 U.	+++	W
21	++++	2500 U.	3500 U.	+	FW
22	++++	2500 U.	5000 U.	++	W
23	++++	2500 U.	3500 U.	+	FW
24	++++	2500 U.	3000 U.	+	FW
25	++++	2500 U.	5000 U.	++	W
26	++++	2500 U.	4000 U.	+	FW
27	++++	2500 U.	4500 U.	+	FW
28	++++	2500 U.	5000 U.	+	W
29	++++	2500 U.	5000 U.	++	W
30	++++	2500 U.	3500 U.	++	FW
31	++++	2500 U.	5000 U.	+++	W
32	++++	2500 U.	4000 U.	+	FW
33	++++	2500 U.	5000 U.	+++	W
34	++++	2500 U.	4000 U.	+	B
35	++++	2500 U.	5000 U.	+	W
36	++++	2500 U.	3500 U.	+	FW
37	++++	2500 U.	4000 U.	+++	B

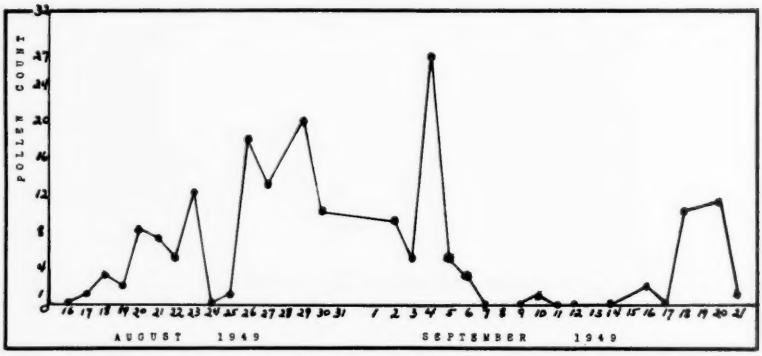


Fig. 1. Ragweed pollen count, 1949. The count represents the number of pollen grains sedimenting in a twenty-four-hour period over an area coverable by a ⅜-inch cover slip. Counts were made on slides exposed in the heart of downtown Boston (Haymarket Square) and tend to be about one-tenth as large as counts made in suburbs. 1949 was an atypical year because it was dry. Counts were made by Dr. Wheeler, of Tufts College Medical School and the Boston Health Department.

these top doses were increased to a much higher level; that is, above 2,500 PN units for Class B, and above 5,000 PN units for Class C patients. For example, a Class B patient who was receiving 2,500 PN units of pollen extract every three weeks during the first year of treatment, was able to receive a maximum dose of 4,000 PN units during the second, third, and fourth years of treatment, thereafter. This was also true of Class C patients whose top dose, as shown in Table I, was 5,000 PN units; it could be raised to 10,000 PN units after the second, third, and fourth years of treatment if given at three-week intervals perennially.

During the first week of October, 1949, all patients who had received perennial treatment for more than one year, at three-week intervals, were retested with 500 PN units of ragweed extract, by the intracutaneous method, in order to determine whether the cutaneous reaction corresponded with that obtained upon testing on first admission. The following results were noted: of thirty-seven Class B patients, sixteen gave a (+) or slight reaction, sixteen a (+ +) or moderate reaction, and five a (+ + +) or marked reaction (Table II). Of sixty-three Class C patients, six gave a (−) or negative reaction, twenty-three a (+) or slight reaction, twenty-five a (+ +) or moderate reaction, and nine a (+ + +) or marked reaction (Table III). The maximum doses ranged, for Class B patients, from 3,000 to 5,000 PN units, and for Class C patients, from 5,000 to 10,000 PN units. All of these top doses were administered at three-week intervals during the year and, during the hay fever season, at two-week intervals.

The ragweed pollen count for Boston, for the year 1949, was made by Dr. Ralph Wheeler of Tufts College Medical School, and of the Department of Public Health of the City of Boston (Fig. 1). The pollen count in Boston this year was atypical because of the fact that it was a very

TABLE III. SIXTY-THREE CLASS C PATIENTS

	Test Reaction on Admission to 500 Units	Top Dose First Year	Top Dose After First Year	Test Reaction After Three Years − 6 + 23 ++ 25 +++ 9	Degree of Improvement W 42 66% FW 18 29% B 3 5%
1	+++	5000 U.	7500 U.	+	W
2	+++	5000 U.	8000 U.	++	W
3	+++	5000 U.	9000 U.	+	W
4	+++	5000 U.	10,000 U.	++	W
5	+++	5000 U.	6500 U.	+	FW
6	+++	5000 U.	8500 U.	−	FW
7	+++	5000 U.	8000 U.	−	FW
8	+++	5000 U.	10,000 U.	+++	W
9	+++	5000 U.	9000 U.	+	W
10	+++	5000 U.	10,000 U.	++	W
11	+++	5000 U.	8000 U.	+	W
12	+++	5000 U.	10,000 U.	+	W
13	+++	5000 U.	7500 U.	−	FW
14	+++	5000 U.	10,000 U.	++	W
15	+++	5000 U.	6500 U.	+	FW
16	+++	5000 U.	8000 U.	−	FW
17	+++	5000 U.	6500 U.	+	B
18	+++	5000 U.	10,000 U.	+	W
19	+++	5000 U.	7500 U.	++	B
20	+++	5000 U.	10,000 U.	−	W
21	+++	5000 U.	8500 U.	++	W
22	+++	5000 U.	8500 U.	+	FW
23	+++	5000 U.	8500 U.	+	FW
24	+++	5000 U.	10,000 U.	+	W
25	+++	5000 U.	8000 U.	+	FW
26	+++	5000 U.	10,000 U.	+	W
27	+++	5000 U.	9000 U.	+	W
28	+++	5000 U.	7500 U.	−	FW
29	+++	5000 U.	10,000 U.	++	W
30	+++	5000 U.	9500 U.	++	W
31	+++	5000 U.	8500 U.	+	W
32	+++	5000 U.	9000 U.	++	W
33	+++	5000 U.	8500 U.	++	W
34	+++	5000 U.	8500 U.	+	W
35	+++	5000 U.	10,000 U.	+	W
36	+++	5000 U.	10,000 U.	++	W
37	+++	5000 U.	8000 U.	+	FW
38	+++	5000 U.	9000 U.	+	W
39	+++	5000 U.	8000 U.	+++	B
40	+++	5000 U.	10,000 U.	+++	W
41	+++	5000 U.	10,000 U.	+	W
42	+++	5000 U.	9500 U.	++	W
43	+++	5000 U.	7500 U.	+++	FW
44	+++	5000 U.	8000 U.	+	FW
45	+++	5000 U.	8500 U.	++	FW
46	+++	5000 U.	10,000 U.	+++	W
47	+++	5000 U.	7500 U.	++	FW
48	+++	5000 U.	10,000 U.	++	W
49	+++	5000 U.	9500 U.	++	W
50	+++	5000 U.	8500 U.	+++	W
51	+++	5000 U.	7000 U.	+++	FW
52	+++	5000 U.	10,000 U.	++	W
53	+++	5000 U.	8500 U.	++	FW
54	+++	5000 U.	10,000 U.	++	W
55	+++	5000 U.	10,000 U.	++	W
56	+++	5000 U.	10,000 U.	++	W
57	+++	5000 U.	10,000 U.	++	W
58	+++	5000 U.	8500 U.	++	FW
59	+++	5000 U.	7000 U.	+++	W
60	+++	5000 U.	8500 U.	+++	W
61	+++	5000 U.	8500 U.	++	W
62	+++	5000 U.	10,000 U.	++	W
63	+++	5000 U.	9500 U.	+	W

dry summer, and also because the count was made in the heart of the city where the pollen count is usually low. If one wishes the pollen count for the Boston suburbs, he should multiply each daily pollen count by 10.

All Class C patients who received maximum doses ranging from 5,000 to 10,000 PN units did well this year, 1949 (Table III). This improvement was established on the fact that a record of the hay fever symptoms was kept for each patient, and the degree of his improvement was record-

ed at each treatment visit. When the patient stated that he sneezed or had nasal congestion on arising during any day of the hay fever season, it was recorded as *slight* hay fever, and that he was doing *well.* When he stated that he had constant congestion of the nose and itching of the eyes several times during any day of the hay fever season, it was recorded as *moderate* hay fever, and that he was doing *fairly well.* When the symptoms were sneezing or marked congestion of the nose and itching of the eyes, thus causing great discomfort throughout the day, he was recorded as having *marked* hay fever, and that he was doing *badly.*

Of the sixty-three Class C patients treated perennially, at three-week intervals, 66 per cent did *well,* 29 per cent, *fairly well,* and 5 per cent, *badly.* Of the thirty-seven Class B patients treated similarly, 54 per cent faired *well,* 35 per cent, *fairly well,* and 11 per cent, *badly.* The patients that faired *badly* were those who did not keep their appointments regularly, at the three-week interval rate (Tables II and III).

All hay fever patients, exclusive of Classes AA and A, when first treated, received immunizing doses of pollen extract every three to four days until a dose of 1,000 PN units was reached. When this dose of 1,000 PN units was attained, the patients were treated weekly until they reached the maximum dose, according to their arbitrary classification, with safety. Following this, injections were given every three weeks during the year, and, during the respective hay fever season or seasons, once every two weeks. After the season was over, injections were again administered at three-week intervals, perennially.

It was noted that those patients who received massive doses of pollen therapy for more than one year, that is, 5,000 to 10,000 PN units of pollen extract, did well during their respective hay fever seasons and showed some reduction in the size of the wheal upon retesting at the end of the season. The reduction in the size of the wheal upon retesting was not the same for all patients, and the relationship between the degree of improvement of the hay fever symptoms in those patients and the reduction in the size of the wheal on retesting was not an absolute indication that the patient was doing well. It was noted that those patients who received massive doses of pollen therapy improved, irrespective of any decrease in the skin reaction upon retesting. Only 2 per cent of all ragweed hay fever patients treated perennially at the three-week interval rate developed constitutional reactions.

It is the general consensus of almost all allergists that there is no way of definitely classifying hay fever patients according to the degree of skin sensitivity. The schedule of the average doses for the various classes, given in Cooke-Stull protein nitrogen units, is an arbitrary one. That is, the subsequent increase of the treatment doses, as shown in Table I, for the corresponding classes, should be gauged from week to week; and more stress should be placed on the presence or absence of a marked local reaction, which, when present, usually develops within ten to

twenty-five minutes after treatment. When a patient develops a marked local reaction after any treatment injection, the dose is reduced by one-fourth for the next treatment.

The advantages of the perennial method of treatment are: (1) its greater elasticity in correcting lapsed treatments, (2) the ability of the physician to observe the patient over a long period of time, thus learning more about his complicated sensitization and the possible presence of other allergies, if any, and (3) the greater tendency to produce more lasting results. There are, of course, disadvantages, and one of them rests chiefly on the fact that many individuals grow tired of receiving treatment all year round. The question as to whether or not to treat patients preseasonally or perennially depends chiefly on the psychological and physical type of patient.

Becker, Rappaport and McArthur[1] stated that there is a decrease in responsiveness to the injected allergen as one descends the forearm. In other words, not all sites of the skin are equally sensitive. This is not really a great handicap when one uses a freshly standardized extract and limits the tests to a certain area of the arm, usually the dorsal aspect, and repeats these tests either in the right or left forearm at all times. There is, of course, much work to be done yet in this field of perennial treatment and its effect on skin-test sensitization.

The ragweed hay fever patients treated were not chosen with the idea of proving that there is a reduction in the skin-test sensitivity following several years of treatment at the three-week interval rate. They were chosen merely with the idea of noting the amount of improvement obtained following such therapy. The results showed that there is no absolute relationship between massive doses of pollen therapy and the reduction in the skin-test reaction, or that the reduction in the skin-test sensitivity has no relation to the degree of improvement. It was noted, however, that patients without any associated allergic manifestations or complications, who received perennial treatment at three-week intervals, on the average did well.

SUMMARY

A study of 100 Classes B and C ragweed hay fever patients was made and the conclusions derived from this study are as follows:

1. There is no absolute proof that there exists any definite relationship between massive pollen therapy and the reduction in the size of the wheal on intracutaneous testing after a period of three to four years, or more, of treatment.

2. Clinical relief was noted in patients receiving massive doses of pollen therapy when the maximum doses ranged from 5,000 to 10,000 PN units, when the injections were given at three-week intervals perennially.

3. The reduction in the size of the wheal upon retesting, after patients had received more than one year of treatment, at the three-week interval

rate, perennially, was not a definite indication of the degree of improvement elicited by these patients.

REFERENCES

1. Becker, E. L.; Rappaport, B. Z., and McArthur, M.: Qualitative studies in skin testing. J. Allergy, 19:317, 1948.
2. Brown, A.: A new plan for applying the specific treatment of pollen hay fever (perennial treatment); preliminary report. J. Immunol., 13:273, 1927.
3. Brown, E. A.: The skin-test blocking antibody responsible to oral pollen therapy and the criteria for its use. Ann. Allergy, 5:402, 1947.
4. Clarke, J. A., Jr., and Leopold, H. C.: Prophylactic treatment of ragweed hay fever—statistical study. J. Allergy, 8:560, 1937.
5. Cohen, M. B.: The immunologic management of a patient with allergy. J. Allergy, 15:274, 1944.
6. Colmes, A.: Perennial treatment of hay fever—comparative study. J. Leb. & Clin. Med., 19:481, 1934.
7. Colmes, A., and Rackemann, F. M.: Further observations on changes in skin tests following specific pollen therapy. J. Allergy, 4:473, 1933.
8. Cooke, R. A.: A consideration of some allergic problems. II. Serologic studies of the skin reacting allergies (hay fever types). J. Allergy, 15:212, 1944.
9. Feinberg, S. M.: Allergy in General Practice. Philadelphia: Lea & Febiger, 1934.
10. Figley, K. D.: Continuous method of hay fever treatment. J. Allergy, 2:39, 1930.
11. Gay, L. N.: Hay fever—methods of treatment. West Virginia Med. J. 30:366, 1934.
12. Hinnant, J. M., and Evans, F. D.: Management of the patient with pollen allergy. Cleveland Clin. Quart., 3:113, 1936.
13. Johnson, M. C.; Alexander, H. L.; Alexander, H. J., and Walker, H. M.: Measurement of circulating ragweed antigen. J. Allergy, 16:261, 1945.
14. Lamson, R. W.; Piness, G., and Miller, H.: Pollen allergy, skin reactions of patients before and after treatment with spring grass pollens. Am. J. M. Sc., 175:791, 1928.
15. Levin, S. J.: The effect of massive pollen therapy on skin-test sensitivity. J. Allergy, 8:26, 1936.
16. Loveless, M. D.: The conjunctival test as a guide to clinical immunity in hay fever. Ann. Allergy, 3:333, 1945.
17. Markow, H., and Spain, W. C.: The effect of consecutive years of treatment upon cutaneous sensitivity in late hay fever. J. Allergy, 4:363, 1933.
18. Markow, H., and Spain, W. C.: Further observations concerning the effect of pollen therapy upon cutaneous sensitiveness in late hay fever. J. Allergy, 6:227, 1935.
19. Naterman, H. L.: The treatment of hay fever by injections of suspended pollen tannate. J. Allergy, 12:378, 1944.
20. Peshkin, M. M.: Critique of the perennial treatment of pollen allergy. J. Allergy, 7:477, 1936.
21. Rackemann, F. M.: Pollen tolerance—its bearing on the treatment of hay fever. J. Allergy, 18:464, 1947.
22. Rockwell, G. E.: Hay fever—a review of the literature for 1945. Ann. Allergy, 4:148, 1945.
23. Shahon, H. I.: Compendio de Alergia Clinica. Aires: Libreria Hachette, 1943.
24. Spain, W. C., and Fuchs, A. M.: Southern M. J., 30:1199, 1937.
25. Sutherland, C.: The perennial treatment of hay fever. M. J. Australia, 2:372, 1933.
26. Sweetster, H. B., Jr.: Multiple sensitivity in hay fever. Minnesota Med., 19:510, 1936.
27. Unger, L.: Perennial vs. preseasonal treatment of hay fever. J. Allergy, 3:548, 1932.
28. Van der Veer, A.: The relative merits of seasonal and perennial treatment of hay fever. J. Allergy, 7:578, 1936.
29. Van der Veer, A.; Cooke, R. A., and Spain, W. C.: Diagnosis and treatment of seasonal hay fever. Am. J. Med. Sci., 174:101, 1927.
30. Vaughan, W. T.: Perennial pollen desensitization. J.A.M.A., 97:90, 1931.

117 Bay State Road (Shahon)

SKEPTOPHYLACTIC SMALLPOX VACCINATION IN CHILDREN

Immunity Without Morbidity

JOHN G. LITTLE, M.D.
Cleburne, Texas

DURING the last four years I have vaccinated for smallpox by a skeptophylactic method, giving the virus parenterally, the first injection subcutaneously and the second seven days later intradermally. On children under ten years of age, when the vaccination is given by this method and at this interval, and using a suitable virus, there has not been a single case that had any fever or morbidity, and each one has obtained an immune reaction on the second injection, consisting of a papule and a small areola. This was done with sixty-nine children, in which Cutter vaccine was used on sixty-four, and Lederle vaccine was used on five. One of the latter group got a moderate amount of induration in the subcutaneous site four days after the intradermal injection was given, but it quickly subsided without morbidity.

Five children were vaccinated by the subcutaneous method alone. Three of them showed no reaction of any kind, and it was presumed at the time that the vaccination did not take. One which had had two such "failures" was checked, however, after three and one-half years with an intradermal test, and got a strong immune reaction, almost severe enough to be called an accelerated "take," but arising in twenty-four hours and subsiding in forty-eight hours more. Her younger brother, who was vaccinated by the skeptophylactic method, was checked by an intradermal test three and one-half years later, and got a normal immune reaction of low grade severity, thus seeming to have a greater immunity than his sister. Two of the five got a moderate amount of induration and soreness of the arm after nine days.

There is a marked difference in the various strains of virus. Several batches of Cutter vaccine were used over a four-year period. The results were uniform and predictable. One batch of Lederle vaccine has been used, and it gave essentially the same results as the Cutter vaccine. But one batch of Sharp and Dohme vaccine was tried on three patients, and proved to be entirely unsuitable for the method. The intradermal injection in each case would seem to give an immune reaction, but it failed to exert skeptophylactic effect on the previous subcutaneous vaccination, and a primary reaction developed in each case after incubation periods of nine days. One of the patients had the intradermal injection after six days instead of seven. Each one of them ran a normal course of a primary reaction with fever, morbidity, swelling, erythema and induration of the affected limb, intensely painful, subsiding in a few days without

Presented at the Sixth Annual Meeting of the American College of Allergists, January 15-18, 1950, St. Louis, Missouri. Dr. Little is an Associate Member of the American College of Allergists.

vesiculation or ulcer formation, and no scar remaining. In one case, after the child seemed well, the intradermal area, which had looked like a normal immune reaction twenty-four hours after being given and had subsided within forty-eight hours, showed recrudescence twenty days later, and twenty-seven days after the initial subcutaneous injection, was very sore for twenty-four hours, then drained a clear thin pus, subsiding three days later. It did not leave a scar. But it was evident that in this case, not only did the intradermal injection fail to provide skeptophylactic effect to prevent the subcutaneous injection from giving a primary reaction, but the subcutaneous injection failed to provide skeptophylactic effect to prevent in its entirety a primary reaction from the intradermal injection, even though it ran a full course of morbidity in the meanwhile.

This led me to try to determine whether the seven-day interval was the most suitable one for spacing the two injections for each to exert the maximum effect on the other. Using Lederle vaccine, I gave the injections five days apart on two children. Each gave what looked like a normal immune reaction on the second injection which appeared in twenty-four hours, each started to subside, then each flared up again. Both gave intradermal nodules about 1.5 cm in diameter, not very sore, surrounded by an area of hyperemia, and neither had sufficient fever for the parents to observe it. One gave an area of urticaria around the intradermal area 4 cm in diameter with intense itching; the other gave a nodule 2 cm in diameter in the subcutaneous area with hyperemia 1.5 cm in diameter in the skin above it, after an incubation period of ten days. It began to subside in two days. Neither got a scar. The conclusion was that five days was not as good as seven days for the two injections to exert their effect on each other.

The method does not work as well in adults, I believe, because adults show more reaction to smallpox vaccination in general.

I have tried the skeptophylactic method in six adults; four of them got the immune reaction on the intradermal injection and had no morbidity; two of them got about 50 per cent of the expected morbidity of usual methods from the intradermal area, with induration, soreness and some fever. One of these had a small vesicle and had a small scar at the termination.

With parenteral vaccination of any kind, either subcutaneous or intradermal, with live virus, a failure to get a "take" of some kind is almost unknown. There is none of the experience of repeated unsuccessful vaccinations on individuals who later prove to be susceptible, and get a full-blown primary reaction. On children it is not unusual, if the subcutaneous injection only is used, for no soreness or induration of any kind to develop, even though the mother has been instructed to watch for and report even minimal symptoms. Yet one such, as I mentioned above, had the immunity three and one-half years later. It was for the purpose

of proving the presence of immunity that I began to give the second injection intradermally in order to evoke the immune reaction as evidence of a "take;" it was only by chance that I happened to select an interval in which the two injections had skeptophylactic effect on each other, and the second injection prevented a primary reaction of the first, as well as the first injection preventing a primary reaction of the second. I believe also that the intradermal injection contributes more to the immunity of the patient than the subcutaneous injection, in the classic conception that the participation of the skin in the process helps to give a greater immunity.

The subcutaneous method alone had been used by me in the treatment of a number of adults for herpes simplex, pruritus ani et vulvae, and allied disorders, before I began to adapt the method to the primary purpose of vaccination. If the individual is immune there will be a small tender area of induration, about the size of a dime, in twenty-four hours, which regresses rapidly. If he has no immunity there will be no soreness for several days and the patient will have fever, similar to the usual vaccination but usually not so severe, and usually without vesicle formation or any scar. The interval before this occurs varies very widely: it may be as early as five days, in which event it is not likely to be intense, or it may be as late as thirty days before it begins. It is almost always at least nine days. If the patient has received several subcutaneous injections before the reaction starts, as in the treatment of herpes simplex, all sites of injection will take part in the reaction at the same time, although it does not seem that the individual areas are as bad or their sum total gives any more morbidity than does a single site. One elderly lady with a neurodermatitis suffered a generalized vaccinia, with several vesicle formations, followed by scabs and scars; this is the only case, either adult or child, I have seen who was left with a scar following subcutaneous vaccination alone. I do not know whether skeptophylactic vaccination, that is, the addition of an intradermal injection seven days after the first subcutaneous injection would have prevented the generalized vaccinia.

I dilute the amount of virus contained in one capillary tube to one cc with saline, and give 0.05 cc at a dose, subcutaneously on the first dose and intradermally seven days later. The child is brought back twenty-four hours after the second injection to read the results.

The method of subcutaneous vaccination is not new, but for some reason there is very little in the present-day literature about it. As far as I know, my addition of the intradermal injection as a check on the immunity and to prevent the development of morbidity is new. Several writers make the statement that the subcutaneous method is the method of choice if smallpox vaccination is imperative in cases of eczema. But the routine use of the method, even though it alone gives much less mor-

bidity than the scratch method alone, seems to have been discouraged by a statement in the literature many years ago that it is more likely to cause encephalitis. This reference is so old that I have been unable to find the original statement, and I do not know whether it is based on an unfortunate experience or on theoretical considerations. It is one of the statements in medical literature passed on from one writer to another without explanation, until the circumstances giving rise to the utterance are lost.

The dermatologists for a number of years have been using smallpox vaccination in the treatment of herpes simplex. Many of them use it subcutaneously or intramuscularly. If there have been any bad results, the reports of such have escaped me.

The intradermal method seems to me to be superior to the scratch method in the second vaccination, because it is so rarely a failure. I have mixed my solutions and kept them in the refrigerator for months at a time, and they still give a good strong reaction. In the Navy I vaccinated 1,200 Marshallese natives by that method after the surrender of Jaluit with vaccine eighteen months out of date as the only vaccine available. The follow-up was poor, but I do not know of a single case that did not get a primary "take," an accelerated reaction, or an immune reaction, according to whether or not they had had a previous successful vaccination by the Japanese. One worker in China reported using it for twenty years, and recommended it above the scratch method for fewer failures, less secondary infection, and less morbidity.

I do not know how long the immunity lasts by the skeptophylactic method, having checked it on only one case after three and one-half years. On a few adults vaccinated only by the subcutaneous route, I have checked and found it still present after four years. I have not had the courage yet to try the skeptophylactic method on an individual with infectious eczematoid dermatitis, but I intend to use it if vaccination seems essential in such a person. I prefer to give it after a child has had a course of tetanus toxoid injections in case the vaccine is contaminated, but believe that on the whole there is less danger of tetanus than with the scratch method because there is no ulcer to invite outside contamination.

The skeptophylactic effect of balancing the difference in rate of reaction of two shock organs, the skin and the subcutaneous tissue, makes one speculate about whether a similar method could be used on other virus diseases. It would be worth trying on measles, which also has a shock organ in the skin as well as systemic manifestations. I suggest that it would be worthwhile trying an intradermal injection of attenuated live measles virus seven or eight days after exposure of the individual to measles.

(Continued on Page 103)

NORISODRINE BY AEROHALOR IN ASTHMA

ROBERT E. KAUFMAN, M.D., and LAURENCE FARMER, M.D.
New York, New York

AN isopropyl derivative of nor-epinephrine, racemic 1-(3′-4′-dihydroxyphenyl)-2-isopropylaminoethanol has many trade names, including Norisodrine, Isuprel, Aleudrine, I.P.A., Isorenin, Isonorin, Neodrenal, and Neo-epinine. The official chemical name is isopropylarterenol. Experimental work demonstrates that this drug has a very powerful bronchodilator effect.[9,10,11,13,16,18,19] Clinical experience has corroborated its value in the treatment of asthma when used orally, sublingually, subcutaneously, or by inhalation of a nebulized mist.[1-8,12,14,15,17,20]

The most recent and most effective method of administration is the inhalation of a dust. The apparatus, technique and clinical effects in twenty-four patients with asthma are fully described by Krasno, Grossman, and Ivy.[12] We used sifter cartridges of 25 per cent Norisodrine sulfate dust, Abbott,* with their Aerohalor. The plastic powder inhaler is easy to use and small enough to carry in the pocket.

Our series consists of sixty-three patients with asthma and one with allergic cough (Table I). The ages ranged from six to seventy-one years, and fifty-two of the cases were considered severe or moderate. Like Gay and Long,[6] we did not classify the patients on the basis of allergenic causation. Some were emphysematous and some suffered from chronic bronchitis in addition to bronchial asthma. Of the sixty-four cases there were excellent results in thirty-nine, good to fair in thirteen, and poor in twelve. Two of the patients obtained no benefit while in status asthmaticus, although the results were good when the asthma was milder. Of the twelve patients with poor results, five did not give the medication a long or varied enough trial to assess its value fairly.

The results in our series are approximately the same as those obtained by Krasno, Grossman, and Ivy. They stated that sixteen of twenty-four patients were controlled by the inhalation of Norisodrine alone and that eight required additional symptomatic therapy. We usually did not add any other drug during the trial with Norisodrine, since we felt that a combination of medication might obscure the interpretation of the results.

Most of our patients took one to four inhalations at one to one and a half minute intervals several times a day, as needed. It appears that the number of inhalations can best be determined by the patient, and will vary with the severity of the attack, the promptness with which the drug is taken, the depth and rapidity of inspiration, the concentration of Norisodrine, the amount of residual powder in the Aerohalor, and the appearance of side effects. Generally not more than four to five inhalations should be taken at one session, and one cartridge should last at least twenty-four hours. The benefit will be greater and the side effects less

From The Allergy Clinic, Lenox Hill Hospital, New York, New York.
*Kindly supplied by the Abbott Research Laboratories, North Chicago, Illinois.

TABLE I.

Cases No., Sex, Age	Severity and Duration of Asthma	Dosage Norisodrine Powder			Clinical Results	Side Effects
		Indiv. Dose Inhal.	Freq. Per Day	Duration of use (wks.)		
1 M 47	Severe 19 yrs.	3-4	3-4	5	Excellent: "best thing ever used"; discarded all other medications.	None
2 F 56	Severe 1½ yrs.	3-4	2-4	3	Fair: 1st wk. q 3-4 hrs. with relief; then had relief for only 1 hr. q. time.	Tachycardia, palpitation, nervousness causing her to stop; didn't try 2 inhal.
3 F 23	Severe 6 mos.	2-4	2-4	6	Excellent; relief in few min. lasting 2-4 hrs.	3 inhal.: tachycardia, nervousness; 2 cause less.
4 M 51	Severe 3 yrs.	2-4	2-3	5	Excellent; relief for 3 hrs. with 2 inhal.	3 inhal.: tachycardia, palpitation, nervousness.
5 M 44	Severe 2 yrs.	2-4	1-2	5	Excellent; "best thing ever used" relief in 2 min. lasting 4-5 hrs.	3 inhal.: palpitation, tachycardia and nervousness; 2 inhal.: no side-effects.
6 F 60	Severe 20 yrs.	2-3	2-4	5	Excellent: relief in few min. lasting 3-4 hr; "best thing ever used."	None; used to get some from adrenaline.
7 F 62	Severe 1 yr.	a. 3-4 b. 6-7	Twice 2-3	1 1	Poor (Status asthmaticus). Good; relief for 2-3 hrs.	None even with 7 inhal.
8 F 58	Severe 6 mos.	2-4	1-2	6	Excellent; "best drug ever used"; relief with 1 inhal. if used early.	4 inhal.: tachycardia & palpitation; 2 inhal.: no side effects.
9 M 45	Severe 12 yrs.	2-3	2	1	Poor; "asthma worse."	Palpitation.
10 F 56	Severe 25 yrs.	3-8	2-3	6	Excellent; "miracle; best thing ever used."	None even with 8 inhal. (½ cart. 16% dust).
11 M 63	Severe 8 yrs.	3	2-3	3	Good; relief in few min. lasting 2-3 hrs.; "quite good."	None.
12 F 21	Mod. Severe 20 yrs.	1-3	1-2	6	Excellent; "as good as best drugs ever used."	2 inhal. occ. cause sl. dizziness and tachycardia.
13 M 64	Severe 2 yrs.	3	2	5	Excellent; "best drug ever used."	Sl. palpitation.
14 M 24	Mild; 6 yrs. (with hay fever).	3	1	3	Excellent; relief in few min.	Sl. dryness in mouth and throat; sl. nervousness.
15 M 71	Severe 3 yrs.	a. 4-6 b. 4-5	5-6 2-4	2 1	Poor (status asthmaticus). Good.	Only slight bad taste.
16 M 60	Severe 15 yrs.	2-3	2-3	5	Poor. Relief good first 2 wks.; then "didn't help much."	Thinks drug caused anorexia.
17 M 15	Mod. severe 8 yrs.	2	1-2	2	Excellent; "wonderful, better than any other drug."	Sl. nervousness for few seconds.
18 M 60	Severe 7 yrs.	3	5-6	3	Good; relief for 1 hr.; "best thing ever used."	Palpitation if he takes more than 3 inhal.
19 F 46	Mild 5 yrs.	2	1-2	6	Excellent; "quickest relief of any drug."	None.
20 M 37	Severe 10 yrs.	4	1-2	2	Poor.	Thinks asthma gets worse.
21 M 16	Mod. 3 yrs.	1	3	10	Excellent.	Palpitation.
22 F 60	Mild 12 yrs.	2-3	2-3	1	Poor; no relief.	Choking sensation.

TABLE I. (CONTINUED)

Cases No., Sex, Age	Severity and Duration of Asthma	Dosage Norisodrine Powder			Clinical Results	Side Effects
		Indiv. Dose Inhal.	Freq. Per Day	Duration of use (wks.)		
23 F 70	Mild 5 yrs.	2-3	2-3	1	Poor; no relief.	Choking sensation.
24 F 65	Severe 5 yrs.	2-3	2-3	1	Poor; no relief.	Choking sensation.
25 M 56	Mild 6 yrs.	2-3	1	1	Poor; no relief.	Dryness in throat.
26 M 50	Severe 4 yrs.	3-4	2-3	2	Fair; relief for 1½ hrs.	None.
27 F 31	Severe 11 yrs.	1-3	2-3	2	Excellent; "Sensational; best thing ever used."	None.
28 F 61	Mild 20 yrs.	4	1	2	Fair; relief for only 1-2 hrs.	None.
29 F 45	Mod. 10 yrs.	3-4	4-5	2	Excellent; relief in 5 min. lasting several hrs.	None.
30 F 38	Mild 25 yrs.	1-5	1	3	Excellent. Relief in few min. and lasts many hrs. Just as good as Adrenalin 1:100.	4-5 inhal. cause tachycardia; 1-2 none.
31 M 49	Mod. 6 yrs.	3	1	2	Excellent. Relief in few min. lasting many hrs. "Best thing ever used."	None.
32 F 35	Mild 20 yrs. (with emphysema)	2-3	1-2	8	Excellent. Relief immed. lasting 2-4 hrs.	None.
33 F 38	Severe 30 yrs.	2-4	1-2	5	Excellent. Immed. relief lasting several hrs.	None.
34 F 54	Severe 12 yrs.	5-6	5-7	7	Good. Immed. relief lasting 1½-2 hrs.	None.
35 F 38	Severe 17 yrs.	1-3	2-5	2	Poor; some relief but side-effects preclude much use.	Tachycardia, palipitaton, nervousness with even 1 inhal.
36 F 50	Mod. 15 yrs. (with hay fever)	4-5	2-4	3	Excellent. Relief in few min. lasting several hrs.	None.
37 F 23	Mod. 2 yrs. (with hay fever)	1-3	1-2	5	Excellent. Relief in few min. lasting many hrs.	Tachycardia, palpitation, nervousness with 2 inhal.; none with 1 inhal.
38 F 45	Severe 3 yrs.	2-3	4-5	5	Good; relief in 5 min., but not always; occ. relief for only 1-2 hrs.	None.
39 M 25	Mod. Severe 23 yrs.	3	3	3	Good; relief quickly for mild attacks but not always for severe attacks.	Cough.
40 F 40	Mild 20 yrs.	2	1	2	Excellent; relief in few min. lasting many hrs.	None.
41 F 27	Severe 2 yrs.	1-3	1-2	3	Excellent; immed. relief for many hrs. "Remarkable; best drug ever used"	None with 1-2; but palpitation and tachycardia with 3 inhal.
42 F 39	Mod. 10 yrs. (with hay fever)	3-4	3-4	5	Excellent; immed. relief lasting several hrs.	None.

TABLE I. (CONTINUED)

Cases No., Sex, Age	Severity and Duration of Asthma	Dosage Norisodrine Powder			Clinical Results	Side Effects
		Indiv. Dose Inhal.	Freq. Per Day	Duration of use (wks.)		
43 F 38	Severe 7 yrs.	2-3	1-2	5	Excellent; immed. relief for many hrs. "Wonderful; better than any other drug."	None.
44 F 25	Severe 20 yrs.	4-6	4	1	Excellent; rapid relief lasting 2-3 hrs.	None.
45 M 8	Severe allergic cough 2-3 yrs.	4-5	3-4	4	Excellent; cough had resisted all other medication except adrenaline inj.	None.
46 M 37	Severe 31 yrs.	1-2	5-6	4	Excellent; relief immed. lasting several hrs.	Slight tachycardia.
47 F 54	Mod. 3 yrs.	1-2	1-3	4	Relief in 5-10 min. lasting several hrs.	Slight nervousness.
48 F 19	Mod. 7 yrs.	3-5	3-4	3	Excellent; relief immed. lasting 3-4 hrs.	None.
49 F 41	Mod. 1 yr.	3-5	1	2	Excellent; relief in few min. lasting many hrs.	None.
50 M 16	Mild 6 yrs.	1-2	1	3	Excellent; relief in few min. lasting many hrs.	None.
51 M 51	Severe 23 yrs. (with emphysema)	3-4	3-5	8	Excellent; relief in few min. lasting few hrs.	None.
52 M 6	Severe 1 yr.	2-3	3-5	6	Good; but result lasts only about 1 hr.	None.
53 M 32	Severe 5 yrs.	2-3	1-2	8	Excellent; immed. relief.	None.
54 M 58	Severe 10 yrs.	4-6	2-3	2	Excellent; relief for many hrs. "Best drug ever used."	None.
55 M 50	Severe 11 yrs.	4-6	4-6	3	Good. Relieves mod. attack quickly but not so effective for severe attack.	None.
56 F 23	Mod. 2 yrs.	1-2	1-2	3	Fair; usually gets quick relief with 1 inhal. if asthma is mild.	None.
57 M 55	Severe 5 yrs.	3 (10%)	4-5	5	Good; relief in few min. for 2 hrs.	None.
58 M 52	Severe 4 yrs.	3-4	6-7	5	Poor; relief for only ¼ hr.	Sl. nervousness.
59 M 38	Severe 4 yrs.	3	3-4	3	Excellent; quick relief lasting many hrs.	None.
60 F 55	Severe 4 yrs.	3	2-3	2	Good; relief lasts 4-5 hrs.	Sl. nervousness and tremor.
61 F 45	Mild 2 yrs.	3-5	2	6	Excellent; quick relief lasting many hrs.	Sl. tremor.
62 F 28	Severe 20 yrs.	4-6	7-8	1	Poor; says she gets no relief.	None.
63 F 19	Mild 3 yrs.	2-3	1	5	Excellent; immed. relief lasting many hrs.; "best drug ever used."	None.
64 F 54	Severe 1 yr.	3-4	4-5	3	Excellent; immed. relief lasting several hrs.	None.

if a small number of inhalations are taken early in the attack. The best procedure is for the patient to take a deep, rapid breath with the lips closed over the Aerohalor, remove it and close the mouth, wait one to one and a half minutes, and repeat until relief is obtained or disagreeable symptoms occur.

Many of our patients consistently terminate an attack with only one or two inhalations taken as soon as tightness in the chest or wheezing is noted. There is usually moderate to marked subjective and objective improvement in one to four minutes after the first inhalation. Judging by patients who formerly used epinephrine by injection, Vaponephrin or epinephrine by nebulizer, or Isuprel by various routes, we can state definitely that to abort an attack 25 per cent Norisodrine dust by Aerohalor is preferred by many patients.

No serious side effects were noted among twenty-four patients treated by Krasno et al nor among sixty-four patients treated by us. The only undesirable symptoms recorded in either group were transitory, and consisted of tachycardia, palpitation, nervousness, dizziness, dryness in the mouth or throat, cough, and in three elderly women a "choking sensation." A few of our patients who at first had excellent or good results reported some diminution in the beneficial effect with continued use.

SUMMARY

1. Sixty-three patients with asthma and one with allergic cough were treated with 25 per cent Norisodrine dust by Aerohalor.

2. There were thirty-nine excellent results, thirteen good to fair, and twelve poor.

3. Over 60 per cent of the patients derived great benefit from Norisodrine, usually requiring no other symptomatic medication.

4. Side effects were all mild and transitory, and were chiefly similar to those seen with epinephrine.

5. In the large majority of cases no diminution in therapeutic effect was noted with continued use.

ADDENDUM

Since this article was submitted for publication, we have treated eleven additional patients having moderate or severe asthma with Norisodrine. There were eight excellent results, one good, and two poor. Approximately 63 per cent of the seventy-five patients in the entire series obtained excellent results. Several individuals preferred the 10 per cent Norisodrine to the 25 per cent strength, stating that it produced fewer undesirable symptoms with almost as good a therapeutic effect.

REFERENCES

1. Bellinger, H.: Ueber die perlinguale therapie des asthma bronchiale. Wien. Klin. Wchnschr., 55:348, 1942.
2. Charlier, R.: La thérapeutique prolongée des dyspnées asthmatiformes par les aérosols medicamenteux pneumodilatateurs. Rev. belge sc. med., 17:42, 1946.
3. Charlier, R.: L'Utilization des aérosols d'aleudrine pour le traitement prolongé de l'asthme. Importance de la rigeur dans l'application de cette thérapeutique. Rev. belge sc. med., 17:108, 1946.

4. Charlier, R.: Therapeutical studies in bronchial asthma with the aerosols of Aleudrin. M. Times, 75:277, 1947.
5. Cohen, E. N., and Van Bergen, F.: Isuprel, a new bronchodilating agent. Bull. Univ. Minnesota Hosp. & Med. Foundation, 19:424, 1948.
6. Gay, L. N., and Long, J. W.: Clinical evaluation of isopropyl-epinephrine in management of bronchial asthma. J.A.M.A., 139:452, 1949.
7. Hajos, K.: Experiences on newer methods of treatment of bronchial asthma. Fortsch. Ther., 19:274, 1943.
8. Herxheimer, H.: Aleudrine and Anthisan in bronchial spasm. Lancet, 254: 667, 1948.
9. Konzett, H.: Neue broncholytisch hochwirksame körper der adrenalinreihe. Arch. f. exper. Path. u. Pharmakol., 197:27, 1940.
10. Konzett, H.: Neues zur asthmatherapie. Klin. Wchnschr., 19:1303, 1940.
11. Konzett, H.: Zur pharmakologie neuer adrenalinverwandter körper. Arch. f. exper. Path. u. Pharmakol., 197:41,1940.
12. Krasno, L. R.; Grossman, M. I., and Ivy, A. C.: The inhalation of 1-(3', 4'-dihydroxyphenyl)-2-isopropylaminoethanol (Norisodrine sulfate dust). J. Allergy, 20:111, 1949.
13. Lands, A. M.; Nash, V. L.; McCarthy, H. M.; Granger, H. R., and Dertinger, B. L.: The pharmacology of N-alkyl homologues of epinephrine. J. Pharmacol. & Exper. Therap., 90:110, 1947.
14. Lowell, F. C.: Curry, J. J., and Schiller, I. W.: A clinical and experimental study of Isuprel in spontaneous and induced asthma. New England J. Med., 240:45, 1949.
15. Quitschal, W.: Die inhalationstherapie bei asthma bronchiale und asthmoiden zuständen bei der chronischen spastischen bronchitis und emphysema. Deutsche med. Wchnschr., 68:942, 1942.
16. Rossler, R.: Neue wege der asthmatherapie. Wien. klin. Wchnschr., 53:974, 1940.
17. Segal, M.S., and Beakey, J. F.: Management of bronchial asthma: The use of 1-(3', 4'-dihydroxyphenyl)-2-isopropylaminoethanol. Ann. Allergy, 5:317, 1947.
18. Siegmund, O. H.; Granger, H. R., and Lands, A. M.: The bronchodilator action of compounds structurally related to epinephrine. J. Pharmacol. & Exper. Therap., 90:254, 1947.
19. Stolzenberger-Seidel, M.: Klinische untersuchungen zur behandlung des asthma bronchiale. Klin. Wchnschr., 19:1306, 1940.
20. Voegtli, W., and Verzár, F.: Beeinflussung von vitalkapazität und atmung durch broncholytisch wirkende spray bei asthma bronchiale und beim normalen. Schweiz. med. Wchnschr., 75:457, 1945.

33 East 65th Street
New York 21

PARA-AMINOBENZOIC ACID DERIVATIVES

(Continued from Page 73)

3. Fraser, R. J.: Intravenous pantothal procaine analgesia. Anesth. & Analg., 27: 159, (May-June) 1948.
4. Herrell, Wallace E.: Penicillin and Other Antibiotic Agents. Philadelphia: W. B. Saunders Co., 1945.
5. Long, Perrin H.: ABC's of Sulfonamide and Antibiotic Therapy. Philadelphia: W. B. Saunders Co., 1948.
6. Northey, E. H.: The Sulfonamides and Allied Compounds. New York: American Chemical Society, 1948.
7. Meyers, C. B.; Van der Heide, E. C., and Balcerski, M.: Exfoliative dermatitis following sulfanilamide. J.A.M.A., 109:1983, (Dec.) 1937.
8. Peck, S. M., and Feldman, J. J.: Dermatitis due to procaine penicillin: J. Invest. Dermat., 13:109-110, (Sept.) 1949.
9. Rogers, E. B.: Sensitization reaction to sulfanilamide. J.A.M.A., 111:220-221, (Dec.) 1938.
10. Schwentker, F. F., and Gelman, S.: Bull., Johns Hopkins Hosp., 61:136, (Aug.) 1937. Quoted by Rogers, E. B.[9]
11. Sollman, Torald: A Manual of Pharmacology. Philadelphia: W. B. Saunders Co., 1948.
12. Squier, T. L.: Personal communication.

1033 Gayley Avenue

DEMEROL HABITUATION IN BRONCHIAL ASTHMA

With Report of a Case

ALFRED ROMANOFF, M.D., F.A.C.A.
New York, New York

DEMEROL (Meperedine Hydrochloride) has had extensive use in the treatment of bronchial asthma. Symptomatic relief in attacks of asthma is often obtained because of the antispasmodic and relaxing effect of this drug. However, the use of Demerol in the treatment of bronchial asthma, particularly in status asthmaticus, has been condemned by some clinicians because of the alleged respiratory depressant effect and the possibility of inducing addiction. We have had considerable experience with Demerol in patients with recurrent attacks of bronchial asthma and in status asthmaticus, given orally or parenterally in doses of 50 to 100 mg three times a day, and occasionally more often, without encountering serious respiratory depression or inducing drug habituation. This is in accord with the observations of Batterman,[2] who administered large doses of Demerol for many months to patients for relief of pain, without causing cases of addiction. It is not to be assumed, however, that addiction does not occur. Anslinger[1] states that the files of the United States Bureau of Narcotics contain cases of Demerol addiction, but it is not clear whether these were cases of primary addiction. Himmelsbach[4] described addiction in morphine addicts deliberately given Demerol over a period of many weeks. Schneck[5] reported the case of a psychotic woman who had previously been addicted to Pantopon and Dilaudid. Curry[3] records a case of primary Demerol habituation in a young man who took large doses over a period of seventeen months; 72 gm were ingested in all, and as much as 1250 mg in one day.

Demerol habituation may give rise to numerous symptoms, some of which are insomnia, nervousness, irritability, muscular twitchings, anorexia, loss of weight, thirst, frequency of urination and nocturia.

The following is the first case of Demerol habituation seen by us, resulting from the use of Demerol for the treatment of bronchial asthma.

CASE REPORT

V. P., a woman, twenty-five years of age, was referred to the Allergy Clinic of Lebanon Hospital for the treatment of her asthma.

Her past history indicated that she had measles, whooping cough, pneumonia and otitis media when a young child. A history of profound psychic trauma in childhood was elicited.

She began to suffer from attacks of bronchial asthma seven years before her admission to the clinic. The attacks were relieved by injections of epinephrine until one year ago. At that time, Demerol was given to her by injection by her family physician. The injections gave her almost immediate relief, but the attacks became more frequent each day, so that multiple daily injections had to be administered.

She was then taught self-administration of the medication by her physician, and she found herself taking as many as six injections (100 mg each) daily for months at a time. She stated that this was the only medication that gave her relief and that all medication such as ephedrine sulfate, Isuprel, aminophylline tablets and suppositories, Nembutal, Amytal and Seconal failed to alleviate her asthma. A short while after the injection of Demerol she feels relaxed, the wheezing subsides, and she falls into a quiet sleep which lasts for about two hours.

She noticed that while on the Demerol medication her appetite became poor, her throat felt dry, weakness appeared, and she lost about 20 pounds. In addition, she noticed frequency of urination and nocturia.

Physical examination revealed a thin, undernourished, anxious, worried-looking young woman. There was nothing remarkable in the physical findings. The chest revealed sibilant and sonorous râles, typical of bronchial asthma. Both deltoid regions showed induration of the subcutaneous tissue and numerous pitting scars (sites of previous injections).

Laboratory Findings

Hemoglobin	85%	White blood cells	9,650
Red blood cells	4,300,000	Polymorphonuclear cells	76
		Lymphocytes	14
		Eosinophils	8

Intradermal skin tests showed positive skin reactions to dust and dog hair.

An attempt to break the patient of her habituation was made, and she was urged to enter the hospital; after much persuasion she consented to go. She was in the hospital scarcely a day when she requested to be released and complained bitterly of her incarceration, adducing irrelevant reasons for not wishing to remain. She cried, complained of feeling jittery, irritable and depressed and insisted upon leaving the hospital after the first day. She returned home, presumably to continue with her injections of self-administered Demerol.

SUMMARY

1. A case of primary drug habituation to Demerol is reported.

2. Habituation (and addiction) to Demerol is not common, but definitely occurs.

3. Demerol should not be self-administered.

4. Administration of Demerol in cases of bronchial asthma should be limited to periods of a few weeks at a time.

REFERENCES

1. Anslinger, H. J.: J.A.M.A., 131:937, 1946.
2. Batterman, R. C.: The treatment of arthritic pain with Demerol, a new synthetic drug. Ann. Int. Med., 22:382, 1945.
3. Curry, J. J.: Habituation to Meperedine Hydrochloride (Demerol Hydrochloride). J.A.M.A., 133:243, 1947.
4. Himmelsbach, C. K.: Further studies of the addiction liability of Demerol. J. Pharm. & Exper. Therap., 79:5, 1943.
5. Schneck, J. M.: A case of addiction to Demerol. Bull. Menninger Clin., 8:122, 1944.

933 Fifth Avenue

DERMATITIS DUE TO PARA-AMINOSALICYLIC ACID

E. J. LUIPPOLD, M.D., F.A.C.A.

Boonton, New Jersey

PARA-AMINOSALICYLIC acid was reported early in 1946, by Jorgen Lehman of Sweden, as having definitely bacteriostatic properties against the tubercle bacillus. He had previously tested more than fifty other derivatives of benzoic acid and found this the most effective. No toxic effects were noted on administration to rats, and his first report covered two years' treatment in humans. The drug was given for eight days, withheld for eight, and then resumed on the same schedule. Many cases showed a prompt fall of temperature, gain in weight, appetite, and hemoglobin, and a decrease in sedimentation rate.

The drug did not become generally available for use except to a few investigators until well along in 1948. Few toxic manifestations were noted, though frequently there was mild nausea and vomiting, and rarely diarrhea, which was believed due to the concentration of the acid or to impurities in the preparation used. Nagley and Logg reported some of these effects in twenty-two out of thirty-seven cases treated, but in only two was it necessary to withdraw the drug, and even in these, only temporarily. Four cases developed hematuria and albuminuria, but three of these cleared on treatment with alkalis, and the condition did not recur on resumption of treatment. There have been no other reports of toxic damage to the liver, kidneys, or hemopoietic system.

PAS has been found to have a synergistic action when streptomycin or dihydrostreptomycin is administered concomitantly, and most cases in this country are presently receiving combined treatment.

Skin reactions from PAS were not reported until Kierland and Carr of the Mayo Clinic described four cases in October, 1949, two with fever concurrently and two without temperature rise. Reactions were severe enough in all four to necessitate discontinuance of the drug. Three cases developed a generalized erythematous, macular, pruritic rash, while in one there was a bullous, erosive lesion. Patch and intradermal tests with a 3 per cent solution on all these patients were negative.

A fifth case of skin reaction is here reported.

G. H., a man aged thirty-four, a sedentary watchmaker by trade, developed a spontaneous pnuemothorax in May, 1947, without history of previous pulmonary infection. One sputum concentrate was reported to contain tubercle bacilli, and the patient was admitted to a nearby state institution. Here extensive work-up, including x-rays, repeated sputum concentrates, and gastric washings, was entirely negative; and two months later, the lung having re-expanded and chest plates being clear, the patient was discharged as non-tuberculous. In July, 1949, he developed what was

Presented at the meeting of the New York Academy of Allergy, May 24, 1950.

From the Community Medical Group, Boonton, New Jersey.

thought to be an acute virus pneumonitis, with high spiking fever and diffuse chest signs, and no response to penicillin. However, after three days of dihydostreptomycin 1.0 gm per day, he became afebrile. The drug was continued for a total of seven days, when the chest appeared completely clear. Several sputa during the acute illness and for some time thereafter showed neither tubercle bacilli on direct smear nor in concentrates. He remained apparently well and was not seen again until October 17, 1949, when he developed a severe sore throat. Numerous sticky râles were present in both upper lobes, percussion note was diminished, and breath sounds were bronchovesicular in character. The pharyngitis, but not the pneumonitis, responded to penicillin. On November 19 chest x-ray was reported as shown far-advanced tuberculosis, without cavitation. The sputum was also positive for tubercle bacilli, both in direct and smear and concentrated specimens.

On November 24, the patient was started on dihydrostreptomycin 1.0 gm per day in four divided doses, plus 12 gm per day of PAS in alkaline solution, together with amphojel. This was apparently well tolerated by the patient, and no unusual gastrointestinal symptoms were noted. On December 13, nineteen days after institution of treatment, the patient first noted a mild, generalized itching without visible skin changes. This became progressively more severe, and three days later began to be accompanied by a swinging temperature running up to 103°. On December 19, twenty-five days after PAS was started, both arms and legs were covered with a pruritic, maculo-papular rash, and both the PAS and dihydrostreptomycin were stopped. The lesions continued to spread, despite local therapy, but the temperature, which had gone to 104° in the late afternoon, immediately began to recede. Benadryl 50 mg every three hours and papaverine HCl 60 mg every two to three hours gave some relief from the itching. Shortly thereafter, desquammation of a branny variety began, and clearing was complete on January 15, four weeks after the PAS was discontinued. Twenty-four hour temperatures were also normal.

Patch tests were done to the dihydrostreptomycin, pure PAS, and the alkalinized PAS. Only the PAS tests showed reactions and these were marked positives. To rule out impurities in the PAS as the cause of the reaction, some of the drug was obtained from a different pharmaceutical house, and the patch test was repeated. This was again positive. Control tests were done on the patient's sister, and on a known allergic individual who exhibited contact dermatitis from many substances, and both of these were negative. There has been no intolerance on the part of the patient to acetylsalicylic acid either before or after the dermatitis. Dihydrostreptomycin therapy has been resumed without recurrence of the rash.

SUMMARY

A case of drug dermatitis from the use of PAS in the treatment of tuberculosis is presented. The skin reactions were severe enough to necessitate discontinuance of the drug. Patch tests proved PAS to be the causative factor.

REFERENCES

1. Kierland, R. R., and Carr, D. T.: Reactions to PAS. Proc. Staff Meet., Mayo Clin., 24:539, (Oct. 12) 1949.
2. Lehman, Jorgen: PAS in the treatment of tuberculosis. Lancet, 1:15, (Jan. 5) 1946.
3. Nagley, M. M., and Logg, M. H.: PAS in Pulmonary tuberculosis. Lancet, 256:913, (May 28) 1949.

SKIN TESTS WITH MIXTURES OF BACTERIAL ANTIGENS AND ANTIHISTAMINES

M. R. LICHTENSTEIN, M.D., F.A.C.A.
Chicago, Illinois

IT HAS been demonstrated that antihistaminic drugs suppress the whealing effect of simple antigens. It has also been amply demonstrated that antihistaminic agents are not effective in suppressing the activity of tuberculin. This study was undertaken to determine whether or not antihistamines suppress the reactivity of other bacterial antigens.

METHODS

Immunogens (extracts made from living bacteria*) were used as the antigens. The following bacteria were represented: *Neisseria catarrhalis; Escherichia coli; Klebsiella pneumoniae; Hemophilus influenzae; Diplococcus pneumoniae,* types 1, 2, and 3; *Micrococcus pyogenes* var. *albus* and *Micrococcus pyogenes* var. *aureus; Streptococcus hemolyticus* and *Streptococcus non-hemolyticus.* Benadryl 1 per cent and Pyribenzamine one half per cent were the antihistaminic drugs used.

Mixtures of the antihistaminic drugs (10, 20, 30 or 90 per cent of the total volume) and the immunogen were prepared. The immunogen similarly diluted with saline was used as a control. Intracutaneous injection of 0.05 c.c. of the mixture and the control were placed about 2 inches apart on the arm. Tests were done on afebrile, ambulatory tuberculosis patients. The reactions of the immunogens on these patients has been previously described.[1] Reactions were read at eighteen, twenty-four, forty-eight, and sixty hours. The transverse diameter of the indurated area was measured and recorded.

One hundred forty-two tests were done on twenty-nine patients.

RESULTS

No significant differences could be seen between the mixtures and the controls. The reactions in both appeared at the same time, lasted for the same period, and, within the usual limits of technique, were the same size.

DISCUSSION

The failure of antihistaminic drugs to suppress the reactivity of the immunogens seems to indicate that the delayed reaction of the bacterial antigens resembles that of tuberculin. There appears to be no good reason to think that the effect of these antigens is produced by liberation of histamine.

CONCLUSION

Antihistaminic agents do not suppress the delayed reactions of the bacterial antigens described when injected together intracutaneously.

REFERENCE

1. Lichtenstein, M. R.: Skin Reaction of Surface Antigens and Bacterial Residues. Ann. Allergy, 8:550-551, (July-Aug.) 1950.

From the Municipal Tuberculosis Sanitarium of Chicago. Dr. Lichtenstein is Chief of Medical Service.

*Generously furnished by Parke, Davis & Company.

SYMPTOMS OF HAY FEVER CAUSED BY ALGAE

II. Microcystis, Another Form of Algae Producing Allergenic Reactions

HERMAN A. HEISE, M.D., F.A.C.A.
Milwaukee, Wisconsin

IN a previous paper[1] a subgroup of *Myzophyceae,* or blue-green algae, was shown to be a cause of symptoms of hay fever in susceptible persons. These algae were classified in the family of *Oscillatoriaceae* and proved to be strongly allergenic. Intracutaneous injections produced positive skin tests, passive transfer tests were positive, and "hyposensitization" was followed by relief of symptoms.

In Wisconsin lakes in August and September streaks of blue-green scum are often seen running parallel to the wind direction; and when the wind is very light, the water near the down wind shore may be densely covered with this scum.

On August 16, 1949, some of this material was collected at North Lake in Waukesha County, Wisconsin. Examination revealed an almost pure growth of algae, which were characterized by indefinite shapes of colonies containing hundreds of densely aggregated cells. The envelope surrounding a colony was gelatinous and inconspicuous. This material proved to be another subgroup of *Myxophyceae,* Family: *Chroococcaceae,* Genus: *Microcystis.*[2] Figure 1 represents a low power photograph of the material used. It will be noticed that the growth consists chiefly of *Microcystis,* although an occasional spiral of *Myxophyceae,* Family: *Oscillatoriaceae,* Genus: *Lyngbya Contorta,* is seen (left center).

ALLERGENIC REACTIONS OF MICROCYSTIS

Some of the scum containing *Microcystis* was dried, and glycerosaline extracts of a 1 per cent solution were made. Similarly prepared extracts of the previously reported *Oscillatoriaceae* were made at the same time. Intracutaneous skin tests on ten persons susceptible to *Oscillatoriaceae* were made, using dilutions from 1:1000 to 1:000,000 of *Microcystic* and *Oscillatoriaceae.* The skin tests using both antigens side by side were identical in each of the ten persons tested. About fifty other persons were tested and failed to react to either antigen.

SUMMARY

It has been previously demonstrated that a subgroup of the blue-green algae, *Myxophyceae, Oscillatoriaceae,* is capable of producing symptoms of hay fever and skin rashes in swimmers, and that skin tests for susceptibility and "hyposensitization" were successful.

Another subgroup of *Myxophyceae,* Genus: *Microcystis,* produces posi-

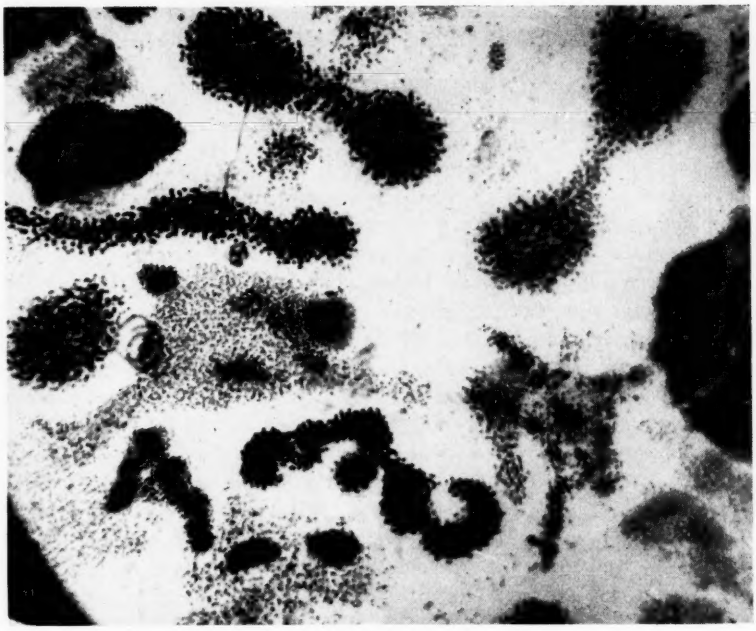


Fig. 1.

tive skin tests in persons susceptible to *Oscillatoriaceae* and fails to react in normal individuals.

Quantitative titrations by skin testing are identical with the two forms of algae.

It may be assumed that the two subgroups of *Myxophyceae, Oscillatoriaceae* and *Microcystis,* contain similar antigens.

REFERENCES

1. Heise, Herman A.: Symptoms of hay fever caused by algae. J. Allergy, 20: 383, (Sept.) 1949.
2. Smith, G. M.: The Fresh-Water Algae of the United States. P. 60. New York and London: McGraw-Hill Book Co., Inc., 1933.

425 E. Wisconsin Avenue

ASSISTANT IN ALLERGY WANTED

An A.C.A. member will need an assistant in the near future. He requires a young doctor, preferably a diplomate in internal medicine, but especially one who wants to make allergy his future career. Beginning as an assistant, he would eventually be assured of the present allergy practice. The location is on the West Coast. An interested, qualified physician may write for further information to the Secretary, American College of Allergists, 423 LaSalle Medical Building, Minneapolis 2, Minnesota.

EFFECTS OF THE ANTIHISTAMINIC DRUGS ON THE ANTIGEN-ANTIBODY REACTION DURING THE ANAPHYLACTIC SHOCK

VINCENZO TRAINA, M.D.
Cleveland, Ohio

IN a recent report[6] it has been shown that in guinea pigs the anaphylactic shock does not occur if they have previously received an antihistaminic inhibited shock. In the above mentioned report the results were interpreted as being due to the fact that at the time of the second shocking injection there were no more antibodies which had already reacted with the antigen of the first shocking injection.

Since it is well known that a release of histamine accounts for the anaphylactic shock in animals,[1,2] theoretically another hypothesis should have been considered: namely, that the antihistaminic protected shock could determine in the guinea pig either a greater resistance to the toxic action of histamine or an increased speed in inactivating it. In order to determine whether or not this might be the case, the following experiments were performed:

Sixteen guinea pigs (medium weight 500 gm) were sensitized with ½ cc of horse serum intraperitoneally. After fifteen days twelve of the guinea pigs were given 5 mg of Benadryl intraperitoneally and fifteen minutes later the shocking injection of 1 cc of horse serum (Squibb) intracardiacally. All of them survived. The next day the four guinea pigs used as controls, which did not receive the antihistaminic protective shock, were given the shocking injection of 1 cc of horse serum intracardiacally. All of them died. Thereupon the twelve remaining guinea pigs were treated as follows: Six of them were given a shocking injection of the same quantity of horse serum intracardiacally. None of them died. The other six guinea pigs were given 1 mg per kg of histamine intracardiacally. This dose is five times the lethal dose of histamine by intravenous injection, the lethal dose being 0.4 mg per kg.[4] All of them died of histaminic shock from the injection within a half hour.

These experiments were repeated using smaller doses of histamine. Six more guinea pigs received in the same manner the sensitizing injection of ½ cc of horse serum and fifteen days later the shocking injection preceded by Benadryl. None of them died. The following day each one was injected with 0.5 mg per kg of histamine intracardiacally. All of the guinea pigs, although showing signs of shock, recovered. These experiments indicate that an antihistaminic protected shock increases in guinea pigs the resistance to a dose of histamine slightly greater than its lethal dose.

According to these results it might be suggested that in guinea pigs which have received previously an antihistaminic protected shock, the ana-

Dr. Traina was associated with Fairview Park Hospital, Cleveland, Ohio, at the time this report was written. His present address is Sacred Heart Hospital, Pensacola, Florida.

phylactic shock does not occur due to the acquired resistance of the animals to a dose of 0.4 mg per kg of histamine, which is the quantity released during the anaphylactic shock.[2,3]

However, this increased resistance to the histamine can be explained only by admitting that during the antihistaminic protected shock, histamine is released, and this can come only from the interaction antigen-antibody. Therefore we can say that the results reported above support the idea already expressed[6]: that the antihistaminic protected shock does not inhibit the reaction between antigen and antibody, although it is difficult to say whether the lack of antibodies or the increased resistance to histamine, or both, account for the tachyphylactic action of the antihistaminic inhibited shock.

REFERENCES

1. Bartosch, Feldberg and Nagel: Arch. f.d. ges Physiol., 230:129, 1932.
2. Code, C. E.: Am. J. Physiol., 127:78, 1939.
3. Dragsted, C. A., and Mead, F. B.: J. Pharmacol. & Exper. Therap., 57:419, 1936.
4. Friedlander, F.; Feinberg, S. M., and Feinberg, A. R.: Proc. Soc. Exper. Biol. & Med., 62:65, 1946.
5. Schild, H. O.: Proc. Soc. Exper. Biol. & Med., 42:494, 1939.
6. Traina, V., and Aleksandrowicz: Nature, 163:364, 1949.

SKEPTOPHYLACTIC SMALLPOX VACCINATION

(Continued from Page 88)

SUMMARY

Sixty-nine children were vaccinated against smallpox by a subcutaneous injection of virus followed seven days later by an intradermal injection. There was no morbidity in any case, no fever, no soreness of the arm, no ulcers or scars, and the second injection in each case gave the immune reaction. Cutter and Lederle vaccine was used; Sharp and Dohme vaccine did not prove suitable for the method. The virus in one capillary tube was diluted to one cubic centimeter with saline, and .05 cc was given at each injection.

The method was successful on four adults out of six in giving immunity without morbidity; the other two had lessened morbidity. Of these one got a very small scar.

113 East James Street

POLLINOSIS WITH INTENSE PRURITUS VULVA

RALPH M. MULLIGAN, M.D., F.A.C.A.

Reading, Pennsylvania

BONNIE B., aged eight, was taken to an osteopath in August, 1945, with intense itching of the vulva, vaginal orifice, and clitoris. There was mild lacrimation, conjunctival pruritus, nasal blockage and rhinitis. The osteopath diagnosed the condition as "imagination," in so far as the genital symptoms were concerned.

In 1946 the child was taken to a pediatrician who diagnosed pin worms, and he in turn referred her to a dermatologist who thought the genital symptoms were due to the drugs that were administered for the pin worms. Ova and parasites were found but anthelmintics and local therapy were of no value. All symptoms disappeared in October. In August, 1947, the symptoms recurred, and the pediatrician again made the same diagnosis. She was symptom-free in October.

On August 26, 1948, the child was brought to my office with pruritus vulva so intense that the child was sleepless and markedly nervous. All lotions and ointments used locally afforded no relief. Among those used were nupercaine, cocaine, alum water, ephedrin and Pyribenzamine ointment. Antihistaminics given orally gave the best results.

Since I was giving the grandmother and the mother ragweed desensitization and in view of the child's minor upper respiratory symptoms and seasonal complaints, intradermals for contacts, inhalants, and pollens were done. Marked reactions were obtained to giant and low ragweed, both direct and by passive transfer. All other tests were negative. Vaginal smears were negative. No *Trichomonas* was found. Gentian violet enseals were administered for pin worms.

It was decided to desensitize the child with ragweed extract. Injections were started in February, 1949, and full dosage was obtained. This past season the child had no itching and very minimal upper respiratory symptoms. It was the first time in five years that she was free from symptoms in so far as the genitalia were concerned. Application of 1:100 ragweed to the genitalia on October 7, 1949, produced moderate itching. Application of a ragweed ointment October 29, 1949, produced intense itching and local reaction.

The following chart measures symptoms for three years on the basis of 1 to 10—the higher the number denoting more severe symptoms:

	Sneezing	Lacrimation	Nasal Blockage	Rhinitis	Pruritus Pharynx	Vaginal Pruritus	Pollen Therapy
1948	2	3	2	1	3	10	No
1949	1	1	2	1	1	0	Yes
1950	1	0	1	1	1	0	Yes

This might well be called "Vaginal Pollinosis."

Progress in Allergy

HAY FEVER

A Review of the Literature of 1949

MORRIS A. KAPLAN, M.D., F.A.C.A., and NORMAN J. EHRLICH, M.D., F.A.C.A.
Chicago, Illinois

Once again we report on the world's literature on hay fever. That this condition is of prime importance, is evidenced in a report by Lazarowitz.[104] He states that it is a public health problem. Three million people are incapacitated from six weeks to years by the common ragweed type of hay fever. About five hundred thousand of this group have evidence of asthma, and it is estimated that about five and one-half million man-work days are lost. It is becoming increasingly difficult to limit the review to the subject as stated, since the title overlaps many related allergic syndromes. We feel that the title should be *pollenosis and fungiosis*. This title limits the review to the above etiological agents and includes the symptoms of all the shock tissues involved. Each year we hope to report some startling discoveries that will make the treatment of pollenosis or fungiosis simple, easily administered, and a more or less complete cure. To date, we cannot report any evidence in the literature of the above, the corticoid steroid hormones notwithstanding. At present, of all the methods advanced, including nonspecific forms of therapy, specific hyposensitization properly administered, is still our best form of treatment.

BOTANY AND POLLEN SURVEYS

A number of pollen surveys were reported this year. Vargas[191] of Ecuador, reported that from October to February the most common pollen belonged to the Gramineae, Amarantheceae, and Chenopod families.

Dumm, Federico, and Zarate[50] report *Anthemis cotula* as a cause of pollenosis.

Vieitez,[193] in a report from Spain, noted that 139 varieties of pollen were causative agents. He presented an analytical key of the pollens reported for the first time from this area. Pollen is in the atmosphere from February to November. Pollens belonging to the families of Gramineae and Cyperaceae are most important.

Marchand[117] reported from Puerto Rico on the pollens that are important in this area.

Sacks[155] studied how far wind-borne pollens can be disseminated. By the use of trans-Atlantic vessels and airplanes, he noted that under favorable conditions pollen can travel at least two hundred miles.

Heise and Heise[83] studied the influence of temperature variations and winds aloft on the distribution of pollens and molds in the upper atmosphere. They call attention to the "lapse rate" as the rate of temperature change with altitude. The reason for this difference is that moist air becomes warmer when its vapor changes to the liquid phase, since the latent heat of condensation is added to the air temperature. Pollens and molds rise into the upper atmosphere to a height which depends upon the lapse rate. A high lapse rate is usually associated with turbulent air. These facts explain the vertical migration of pollens. The influence of winds aloft on the concentration of pollens is of minor importance compared to the lapse rate. By these facts it is possible to prophesy pollen counts twenty-four hours in advance.

Shure and Harris[136] point out that ragweed pollen cases will be in trouble in southern California from western ragweed, bur ragweed, and slender ragweed

pollens. Also, the ordinary grass and weed case of the East will sooner or later have hay fever in California from February through November.

Durham's[52] excellent survey points out that many national parks have little or no ragweed, but that Everglades and Isle Royale National Parks are the only ones east of the Rocky Mountains that can be recommended as a refuge from ragweed pollen. Glacier National Park is a better ragweed refuge than Rocky Mountain National Park.

Pady and Kelly[130] report on the use of silicones in aerobiology. They claim that silicone grease is preferable to vaseline for trapping pollens and fungi, since this compound retains its physical properties from —75 degrees Centigrade to 200 degrees Centigrade.

Newland reports[127] on a method of incorporating a basic fuchsin stain with a plastic Elvanot 71-24 for mounting and staining pollens permanently and rapidly.

Other reports of importance are phenology of British hay fever plants by Hyde,[85] hay fever by Frankland,[67] and a note on ragweed in Honolulu.[92]

Wade's[195] report on atmospheric pollution discusses the present position and the outlook for the future. This report is of importance, as it points out problems dealing with pollenosis.

FUNGI

Surveys on airborne fungi continue here and abroad. An international survey headed by Feinberg for the Research Council for the American Academy of Allergy[121] reported on a program involving some fifty allergists and bacteriologists. They will cover forty states, Canada and Mexico. Harris will compile the results. This is similar to the studies reported by the Association of Allergists for Mycological Investigations.

The New Jersey Allergy Society Committee on Aerobiology, headed by Schaffer,[148] reported on a projected survey for fungi using Well's air centrifuges. Six widely separated sites in the states are to be used. This survey will also study pollen, bacteria, chemical contaminants, and meteorology. If fungi are found in quantity, extracts are to be made and sent to members for clinical testing and evaluation.

Kaplan[95] reported on a survey of airbone fungi of the Boston area in relation to inhalant allergy.

Walton[196] reports from Winnipeg that molds are of the seasonal and unseasonal varieties. Of the seasonal varieties, species of *Alternaria, Hormodendrum,* and *Helminthosporium* were recovered. In addition, rust and smuts of wheat, oats and barley were found. Of the unseasonal varieties, yeast, *Penicillium, Lycopodium, Mucor, Monilia, Rhizopus,* and *Aspergillus* were recovered.

Passarelli, De Maranda, and De Castro[131] report on a study of the incidence of airborne fungi in the city of Rio de Janeiro. They noted that the most commonly found groups of molds were yeast (Saccharomyces type), *Hormodendrum, Rhodotorula, Penicillium, Aspergillus* and *Fusarium,* making up 88.9 per cent of the total fungi. Seasonal incidence was noted particularly for *Hormodendrum* and also for *Rhodotorula* and *Penicillium.* Highest numbers and seasonal frequency coincide with the months from May to October, that is, from the end of autumn through winter to the beginning of spring.

IMMUNOCHEMISTRY

A number of general discussions of note have been published this year. The following are sufficiently interesting to be read completely: Bernton's[15] review of the chemical approach to allergens, Dammin and Bukantz's[45] modification of biologic response in experimental hypersensitivity, Haurowitz's[81] biological problems and

immunochemistry, Kabat's[94] immunochemistry, Raika's[143] theoretical basis of allergy, and William's[200] phylogenetic concept of allergy.

Coulson, Spies and Stevens[38] noted that antigenic fractions containing high amounts of carbohydrate were efficient sensitizers, suggesting that carbohydrate enhances sensitizing capacity of proteins.

Bieberdorf and Argabrite[16] discuss a method for extracting molds grown on artificial media, thus avoiding the use of peptone. The extracts were not irritating, and were more potent than former extracts containing the same amount of nitrogen.

Prince[134] reported on preparing an *Alternaria* extract which is very potent by the use of acetone precipitation of an aqueous extract of *Alternaria*.

Several investigators have reported on the specificity of the skin-test antibody and the blocking antibody. Needless to say, articles which continue to appear showing cross reactions and neutralization of unrelated and related species are confusing.

Budd and Freeman[28] report that grass pollen tends to diminish skin tests to other grasses by hyposensitization. However, in some patients with positive skin reactions to trees and compositae, they note that the skin reactions are reduced after therapy with grass pollen.

Fitzgerald and Sherman,[64] in their article on the specificity of blocking antibody induced by grass pollen extracts, note that whereas patients develop protection by specific hyposensitization, specific blocking antibodies were developed with either one or all grass pollens. The degree of blocking antibody was not constant for all grasses used, and didn't show any constant pattern with one antigen. Blocking antibodies were developed in a normal person after injection of massive doses of grass pollen extract. Blocking occurred against related grasses as well as the one used for the stimulation of antibodies. The skin test remained negative. In allergic patients showing negative skin tests to grass, a positive skin test was induced by pollen injections without the development of any clinical symptoms. Concomitant with the development of skin test was the development of blocking antibodies.

Wodehouse had noted the above reactions and reported them in a previous paper. Last year he also reported on the origin of patterns of allergic sensitization. In this present article,[206] he shows that various related and unrelated allergens may cross neutralize; also, that there is a dominance in sensitization patterns. This is thought to be a function of the relative amounts of the specific reagin present in the serum. He also feels that allergens of subordinate sensitizations neutralize each other reciprocally or unilaterally, regardless of biologic relationships.

Franklin and Lowell[68] could not affirm the report of Squier. They found that ragweed pollen extracts did not destroy *in vitro* white cells from ragweed-sensitive patients.

Yonkman and Mohr[210] report on the use of an antihistaminic agent to prevent epinephrine fastness. They feel that it can be explained on the basis that in patients who are adrenaline-fast, excessive amounts of histamine are released by the injections. In such cases the intravenous administration of antihistaminic drugs would neutralize the excessive amounts of histamine.

Hampton and Johnson,[77] studying deterioration of ragweed pollen extracts, noted that the best prevention of deterioration is the addition of glycerine in equal parts, so that the final concentration is equal to 50 per cent. In such a concentration, temperature did not affect the solution.

Bukantz, Johnson and Hampton,[30] in a series of investigations, reported that refrigeration carried the precipitation of ragweed extracts to completion and there was least avidity for ragweed extract for rabbit anti-ragweed in the region of considerable antibody excess. Heating and freezing showed loss of activity as measured by their ability to precipitate anti-ragweed rabbit serum and to neutralize skin-sensitizing antibodies of human ragweed-sensitive serum. The 50 per cent glycerine extract showed no such loss.

Prince, Arbesman et al[135] demonstrated that the dermatocaeous molds seem to contain group antigens as well as generic or possibly species antigens.

Figley and Rawling[63] report on the use of a concentrated extract in the treatment of mold-sensitive patients. This concentrated extract is much more specific and has greatly simplified the diagnosis of *Alternaria*-sensitive patients.

Keeney and Eriksen[97] report on the chemical isolation and biologic assay of extracellular antigenic fractions.

Weil and Rose,[199] in studying the effects of ammonium salts on the antibody-antigen reaction, note that they do not affect the combining of antibody and antigen as evidenced by the fact that desensitization can be obtained in their presence.

Warren and Dixon[198] report on a most interesting investigation of antigen tracer studies in anaphylactic shock. They found that in the guinea pig, significant amounts of labelled antigen were picked up only by the liver and the lung in anaphylactic shock. They present evidence that the site of antigen location is in the edematous zone of the bronchial musculature. It seemed possible to them that antigen-antibody reaction was related to edema formation.

STANDARDIZATION

The subject of standardization remains one of our major problems. Little has been added this year. Biological standardization and protein and nitrogen content of allergenic extracts are useful methods but do not express the entire picture. Cross reactions *do* occur in skin-testing as evidenced by the work of Wodehouse.[206] Realizing how difficult it is to evaluate skin-test procedures because of the inadequate methods of standardization, one must view with caution the number of papers dealing with skin-testing.

Strauss and Spain[186] report on a single apparatus for defatting, storage, and extracting of antigenic substances.

Dilks and Wolfe[48] report on the effect of seitz filtration on the protein content of allergenic extracts. They reveal that large amounts of protein are lost. It has been felt for a long time that seitz filtration is not completely desirable, because of the loss of protein material during filtration.

Seltzer[176] describes a simple method of improvising droppers for scratch tests. He uses a No. 19-gauge or 20-gauge needle upon which is mounted a rubber bulb from small-sized medicine droppers.

Kleinman[99] describes an adaptor for the rapid performance of puncture skin tests. He believes this method is especially useful in children. This method is a modified intradermal skin test and should be used, we believe, with caution, only after scratch testing.

Rappaport and Becker[144] report on quantitative studies in skin testing. They point out how important it is to have a syringe that can deliver a specific, accurate amount. Such a syringe, which expedites the accurate intradermal administration of small volumes of fluid, is described. Those interested in studies on standardization would do well to read this article.

Maietta[115] describes a syringe which he has devised to facilitate the calculations involved and to insure accurate dosage when two different solutions are to be given from the same syringe.

An excellent general review on skin-testing has been reported by Mitroni.[125] It is written in Spanish.

Some investigators have reported that skin-tests are not reliable. Arner[5] reported on the provocation of allergy by the inhalation of allergens. Abram[2] reported on the use of conjunctival testing in extrinsic respiratory allergy. In a number of patients in whom skin-tests were negative, the use of the conjunctival sac technique proved them positive.

Shulman[177] reported on the use of ragweed ointment in determining seasonal

variation of ophthalmic sensitivity. A large percentage of the cases tested showed a rapid diminution of eye sensitivity, concomitant with a rising tolerance of pollen dosage.

Walzer[197] reported on the evaluation of the electrophoretic method of testing. The investigator found that skin-testing by electrophoresis is preferable as an experimental procedure to the intracutaneous technique.

Blanton and Sutphin[17] reported on a death during skin-testing. On the third series of intracutaneous tests performed after preliminary scratch tests, the patient suddenly complained of air hunger, and became cyanotic and severely dyspneic. Wheezing was audible. She was immediately given adrenaline and morphine. Death occurred in fifteen minutes. It is obvious from this report that we must use every precaution in performing skin-tests with known powerful allergens.

It has been our impression that accurate skin-testing can be accomplished only with pure antigens. Numerous papers in the past have reported on the multiplicity of antigens in short ragweed pollen as demonstrated by the technique of Oudin. They identified at least five antigens.

Rinkel[149-151] reported a series of articles on serial dilution skin-testing. It is his contention that this is the best method for evaluating proper dosage. He states that he hasn't had a single constitutional reaction in his performance of co-seasonal skin-testing for therapy. We cannot help feeling that this is not the complete answer, but the skill and care taken in the performance of this type of testing will help everyone in avoiding overdosage and constitutional reactions.

DIAGNOSIS

Williams and Williams[201] reviewed 300 cases of allergic patients. From these they discuss the natural history of asthma. Many interesting points dealing with hay fever are brought out.

Von Fraenkel[194] discusses the relationship of humidity and allergy, revealing much information.

Greco[73] reports on the low incidence of hay fever in Brazil.

De Castro,[46] discussing the etiological factors in allergy, reports on the rarity of hay fever in Brazilian Negroes. He also notes that of the number of individuals having allergy, only a small percentage of them were Negroes. This is not true in the United States.

Wittich's[203-205] articles stress the importance of molds as a causative factor in hay fever. He feels that the analysis of house dust, spore allergens, and pollens reveals the existence of a common polysaccharide-amino acid compound.

Levin,[107] a technician, has an excellent general discussion of molds from the standpoint of a laboratory technician.

A number of investigators have written excellent papers on molds. Grinnell,[74] Prince,[134] Epstein, Dutton,[53] Maietta,[113] Morrow, and Thiers' reports are valuable.

The ever-increasing interest in mold allergy is evidenced by the number of questions asked in "Queries and Notes"[140-142] in the *Journal of the American Medical Association.*

Leopold[106] writes on "Summer Mysteries," dealing with symptoms of pollenosis. We believe in the axiom "Seek and ye shall find."

Heise[82] reports symptoms of hay fever due to algae growing on a lake in Wisconsin.

Schutzbank[168] discusses climatotherapy in relation to allergy and sheds light on what changes of environment and climate will do.

DRUGS

A number of drugs have been introduced for the treatment of pollenosis. Brown and Ruskin[25] have reported on the use of cevitamic acid in doses of 250 mg three

to four times a day. Fifty per cent of sixty hay fever patients showed upwards of 50 per cent improvement. They reported safety and no side reactions with doses of 1000-2250 mg daily.

Isuprel has been studied by Lipman,[109] Howell, Curry and Schiller;[84] Krasno, Grossman and Ivy.[100] The consensus of the investigators was that in mild cases of asthma, Isuprel gave fair results.

Orthoxine has been reported on by Curry, Fuchs and Leard;[43] Schiller, Lowell, Franklin, and Denton,[163] and Wittich.[202] The consensus of opinion noted was that 200 mg of Orthoxine gave comparable results to 30 mg of ephedrine sulphate. Wittich[202] reports that children tolerate syrup of Orthoxine containing 37 mg to the teaspoon very well. Schiller et al[163] reported preference for ephedrine over Orthoxine. The side reactions with comparable doses of Orthoxine was definitely less.

Major[124] reported that Khellin, the active principle extracted from the seeds of the umbelliferous plant Ammi visnaga, is beneficial in relieving asthma.

Beakey, Bresnik, Levinson, and Segal[12] reported on the use of atropine, bellafoline, and scopolamine in inhibiting bronchospasm.

Mancke and Orzechowski[116] used intravenous novocaine injections in the treatment of asthma with fairly good results.

Schapiro and Sadove[159] were able to completely relieve a patient with intractable asthma by the oral administration of procaine hydrochloride. Our experience with this compound alone or in conjunction with cevitamic acid has been poor.

Boure[20] reported on the excellent effect of vitamin C in immunity.

SPECIFIC THERAPY

The best form of therapy in hay fever or pollenosis is specific hyposensitization. Many of the criticisms of this type of treatment deal with the long and prolonged therapy, the local and constitutional reactions encountered. The question of low dosage or high dosage depends on the individual patient and the location in which the patient is treated. Where the average daily pollen concentration is high, the best results will be obtained with higher doses, avoiding overdosing as evidenced by either marked local or slight to marked constitutional reactions.

Feinblatt and Love[59] report their studies on oral pollen absorption by passive transfer studies. This type of work has been done several times before. Using hydrolyzed pollen which they claim does not upset the gastrointestinal tract, they report their work on the basis of passive transfer studies. With the use of this preparation, Feinblatt and Love[60] feel that this method is practical.

Studies by Schulman and Fuchs[167] using pollen in conjunction with iron alone or in combination with Trimeton found that these combinations had no therapeutic value in hay fever, nor does iron enhance the action of Trimeton.

Maietta[114] using combinations of pollen and antihistamines reports excellent results with this form of therapy. He claims that fewer injections are necessary, larger doses may be given, and constitutional reactions are avoided.

Many general discussions are available, but they add little to what is already known.

Segal[175] has written a very comprehensive paper on this subject.

To the proponents of small doses in hay fever, the report of Ashley[10] should prove most interesting. We cannot subscribe to this type of therapy, for we have found that larger doses are necessary to adequately protect our patients in the Midwest.

Bruun[27] notes, in his studies on hyposensitization, that a 33 per cent error alone is introduced by the use of hypodermic therapy. Interesting enough is his report that one third of his controlled group improved on placebo hypodermic therapy.

Woods[208] states that pollen desensitization is a primary problem of the allergist.

Doyle[49] desensitizes his pollen patients by the intradermal injection of pollen into

the nasal mucous membranes. He states that his results by this method are better than by the parenteral route.

NONSPECIFIC THERAPY

Zeller,[211] Feinberg and Bernstein,[57] Schwartz and Leibowitz,[170] Brem and Zonis[22] are among a number who reported on the use of Pyribenzamine solution locally or nebulized in the symptomatic treatment of pollenosis. Solutions varying from 0.5 per cent to 2 per cent were used with varying success. Little or no reactions were noted. In our hands very little benefit was noted with this type of medication.

Fenton and Huffman[61] introduced Pyribenzamine hydrochloride by iontophoresis. Using 2 to 5 per cent solution, saturated packs of Pyribenzamine solution were introduced into the nose. Treatments averaged eight minutes to each side of the nose with the current varying from three to seven milliamperes with half wave galvanic current. Controls were used with distilled water or normal saline. Cases were treated twice weekly. Slight side reactions occurred. Dizziness in 50 per cent and drowsiness of 20 per cent were noted in the treatments given. This method was found efficacious in those who have marked nasal reactions following the use of vaso-constricting nose drops.

Russell[154] reported on the treatment of hay fever by injection of the nasal mucosa with alcohol. The nose is first sprayed with adrenaline and then locally anesthetized with cocaine. This is followed by the injection of 70 per cent alcohol in the mucosa. The author states that he obtained relief in most of the patients for a period of three to four years.

ACTH has not borne out the expected results first reported in experimental trials by Bordley et al.[19]

Schwartzmann's[174] investigation on the use of synthetic haptens (polysaccharide amino acid complexes) for the treatment of allergy needs further studies.

ANTIHISTAMINES

After the rather wide and generalized use of the currently available antihistaminic drugs, it is apparent that though they are valuable agents for producing symptomatic relief in the management of some allergic diseases, the results obtained have not measured up to the earlier enthusiastic clinical claims for these substances. Their deficiencies include failure to benefit certain types of allergic manifestations, failure to relieve moderately severe and severe allergic symptoms, failure to produce relief of sufficient degree and duration, and the occurrence of numerous and sometimes serious toxic side reactions.

It is significant that, at the annual meeting of the Council on Pharmacy and Chemistry of the A.M.A.,[90] the status of antihistaminic preparations was reviewed and the Council agreed that it would be wise to consider criteria for the acceptance of any new antihistamines. Suggested for consideration were the following criteria: (1) that the drug have a greatly increased potency over those now available, so that it would be possible to give relief to certain allergic manifestations not relievable now; (2) that the drug be much less toxic than any now available; (3) that the drug be more active for a much greater duration, (4) that the drug have other than histaminic action, such as sympathomimetic action or other action that in some way interferes with the allergic mechanism. These criteria are not intended to serve as means of limiting Council acceptance, but as objectives for researchers and manufacturers.

Friedlaender and Friedlaender[70] briefly reviewed the recent development of antihistaminic drugs, their uses and abuses, concluding that although they are useful and helpful in relieving certain allergic symptoms, they are often less effective than older symptomatic drugs in the relief of others. Their use by no means eliminates

the need for an immunologic study of each case of allergy, since it is only by careful attention to the etiologic factors involved that permanent or long-standing relief is possible. As an adjunct to specific treatment the antihistaminic drugs represent a valuable addition to the list of effective anti-allergic measures. Dunlop[51] reviewed the subject of these drugs and concluded that they are of great value in superficial allergies, characterized by vascular reactions in the skin and mucous membranes, resembling the effects produced by the local applications of histamine; but are of little or no value in the treatment of the more deep-seated allergies. It may be that in some visceral allergies histamine is released in such intimate contact with the effector cell that antihistamines are impotent to block its action or it may be that histamine does not play a part. In the Canadian literature Paterson[132] presented a concise review of the antihistamines and their application to allergy. He concluded that although they afford symptomatic relief only for certain allergic manifestations they have won a fine place in modern therapeutics. However, he raises several points of interest that bear further investigation: namely, while giving relief, do they interfere with the antigen-antibody reaction or with desensitization? (Meier and Bucher[122] demonstrated that Antistine does not inhibit antibody production stimulated by repeated antigen injections; in fact, animals given Antistine had a higher antibody titre). Do they cause long-term or remote toxic effects? Is some other principle active in producing symptoms of allergy and anaphylaxis? In a review of hay fever in the British literature, Frankland[67] stated that some recent observations suggest that, when an antihistaminic drug is used as the sole form of treatment, a proportion of such patients may develop asthma toward the end of the pollen season. A true statistical analysis of this would seem to us to be very important, since if true, then the promiscuous use of antihistaminics by patients and its haphazard prescription by physicians should be interdicted. Lachaux[102] presented an interesting review of the activity of histamine and the antihistamines, including their structure, physiologic properties, and mechanism of action.

The therapeutic and side effects of six histamine antagonists were evaluated by Loveless and Dworin,[110] in a group of 113 ragweed hay fever patients. The drugs in question were Antistine, Decapryn, Neo-Antergan, Pyribenzamine, Thephorin and Trimeton. Of these Pyribenzamine and Trimeton produced about the same degree of control of symptoms—from 75 per cent of the severe to 90 per cent of the mild attacks responded to either drug. Neo-Antergan and Decapryn were somewhat less effective, relieving 60 per cent of the severe and 80 per cent of the mild attacks. Inadequate trials with Thephorin and Antistine suggested lower potency. These latter two agents caused the least side reactions, whereas Decapryn was the worst offender. Among seventy patients evaluating two to six drugs, Pyribenzamine and Trimeton were the drugs of choice in a majority of these patients.

Harris[79] observed a group of patients manifesting a variety of commonly encountered allergic manifestations and noted the effects of a few antihistamine preparations, and attempted to evaluate them. He concluded that the responses to the drugs were variable and inconsistent. (The drugs used were Pyribenzamine, Benadryl, Hydryllin, Comp. 1695, and Histadyl.) He felt that of the five antihistamines employed there wasn't much choice as to which was better than the others; all of them were of some palliative value in pollenosis.

Kugelmass[101] evaluated three antihistamines (Diatrin, Benadryl, and Pyribenzamine) in allergic disorders of infants and children. Seasonal hay fever in its mildest form was controlled by these preparations alone, and in the severe cases by a combination of specific immunization and antihistamines. Toxic reactions were observed in a total of about 25 per cent of the cases. Diatrin was more effective in smaller doses and better tolerated than Pyribenzamine and the latter more than Benadryl at each age level. All of the fifty-six children studied who had hay fever were receiving desensitization therapy; hence the antihistamines constituted adjuvant therapy.

In Queries and Minor Notes,[137] in answer to a request for discussions of the antihistamines, the various ones available were listed with comments as to their apparent efficacy and incidence of toxic side effects. They commented that usually the therapeutic efficacy decreases as the side actions are diminished, and quoted Feinberg as stating that Pyribenzamine appeared to have the greatest potency with the least undesirable effects. It was further advised that the lowest dose which will control symptoms should be used, since these reactions appear to be a function of the dose administered.

The comparative toxicities and incidence of side effects of Benadryl, Pyribenzamine, Neo-Antergan, Antistine, Histadyl, and Neohetramine were studied by Schwartz.[169] The dosage levels of each drug was adjusted to give equal therapeutic results in 781 allergic patients. Side effects occurred with all six drugs. Drowsiness, the commonest side effect, was most frequent and pronounced with Benadryl. In contrast, it occurred rarely and was least pronounced with Neohetramine. The overall incidence of side reactions was as follows: Benadryl 61.3 per cent in 217 patients, Pyribenzamine 35.7 per cent in 126 patients, Neo-Antergan 24.8 per cent in 141 patients, Antistine 22.7 per cent in ninety-seven patients, Histadyl 20 per cent in eighty-nine patients, and Neohetramine 7.2 per cent in 111 patients. It is apparent that Neohetramine was the least toxic in therapeutically effective doses.

Dickstein[47] reported on the results of a controlled study in a group of severe ragweed hay fever patients. All subjects were undergoing specific hyposensitization therapy, and their symptoms were previously satisfactorily controlled by either Benadryl or Pyribenzamine. At the height of the pollen season with the count being 500 or more, Antistine was substituted for either Benadryl or Pyribenzamine in seventeen patients. His data showed that Antistine caused unfavorable side effects in only one patient (6 per cent). In the same group Pyribenzamine gave objectionable side effects in 18 per cent and Benadryl in 29 per cent. Satisfactory relief was obtained in 29 per cent of the patients with Antistine, in 64 per cent of the patients taking Benadryl, and in 88 per cent taking Pyribenzamine. Of course one fallacy inherent in any such study is the fact that although a drug may give good results with moderate pollen counts, it fails when the season is at its height, especially in severely afflicted patients.

An excellent review on antihistaminic therapy in general was presented by Loveless and Dworin,[111] and they felt that the published experience with antihistaminic compounds strengthens the concept that histamine plays a role in anaphylaxis and allergy. The mechanism of action is that of a blocking agent, which prevents histamine from gaining access to the receptor cell. In summarizing the clinical reports on eleven antihistaminic drugs, their greatest usefulness was found in urticaria, being 82 per cent effective. Hay fever responded in nearly 75 per cent of the cases. The published reports would suggest that of these eleven agents, Trimeton, Decapryn, Pyribenzamine, Thephorin, and Benadryl may be more effective than the others. In man the most prominent side effect was sedation; others were gastrointestinal disturbances, central nervous system symptoms, dizziness, headache, vascular disturbances, and, in one per cent, allergy to the drugs. Six antihistaminic drugs (Benadryl, Pyribenzamine, Antistine, Neo-Antergan, Neohetramine and Thenylene) were compared experimentally and clinically by Friedlaender and Friedlaender[69] to determine any correlations which might exist. In guinea pigs wide differences in antihistaminic activity were noted when the drugs were compared on the basis of protective action against multiple lethal doses of histamine. Less variation was apparent when comparison was made against one lethal dose. The relative order of efficacy was the same by both methods. Results in antianaphylactic experiments followed the pattern shown in the histamine studies. Variations in the ability of these drugs to reduce histamine wheals in the human skin were comparable to differences observed in guinea pig experiments. Clinical differences between the six drugs tend

to parallel experimental differences, but not necessarily in the same proportion. Quantitative differences shown experimentally are not identical in clinical experience. One compound which proves itself several times more active than another is usually not of increased clinical effectiveness in the same proportion. There are also many instances where a patient will respond more favorably to an equivalent amount of a generally less active drug.

Schwartz and Wolf[173] objectively compared various antihistaminic drugs in humans by the multiple scratch test. Comparisons were made with Pyribenzamine and Neohetramine; Pyribenzamine and Thephorin; Antistine, Neo-Antergan and Pyribenzamine; Histadyl, Benadryl and Pyribenzamine. From their results the drugs can be arranged into three groups as far as antihistaminic properties are concerned. Neo-Antergan, Histadyl, Pyribenzamine and Antistine were more effective in a significant proportion of cases than Benadryl, which is itself more effective than Neohetramine and Thephorin. They felt that the differences between the members of the group are not significant enough in their series to permit adequate rating, if indeed one is better than another. They felt that it is probable that only when the stimulus is much stronger than that occurring naturally can any significant differences be exhibited.

Bain,[11] in the *Proceedings of the Royal Society of Medicine,* presented methods of comparing the weight for weight potencies, relative duration of action, and relative therapeutic efficacies of histamine antagonists. Statistical treatment of the data was omitted. He found Phenergan to have outstanding potency and duration and suggested its suitability as a standard for comparison. The drugs studied were Phenergan, Antistine, and Neo-Antergan. Considered on the basis of potency he felt that Phenergan was seven times more potent than Neo-Antergan and fifteen times more so than Antistine. Duration of action occurred in the same order but the difference of magnitude was not as great. Therapeutic potencies of only Phenergan and Neo-Antergan were compared. The former appeared to be fourteen times more potent when used in twenty cases of urticaria; the apparent differences that were noted in these experiments were differences of degree.

Blumenthal,[18] reviewing the use of antihistaminic drugs in the treatment of hay fever, believes that although they are a valuable addition to our methods of treatment, they are often not efficient and have serious side effects. A large percentage of patients will get relief with one or another in an appreciable degree. The preferred method of treatment, however, is the combined method of hyposensitization with the antihistaminic drugs. Further commenting on the use of histamine antagonists, he stated that the side effects are a very real and serious obstacle, and often the patient changes one set of symptoms for another. The itching, rhinorrhea, and eye symptoms are much more relieved than the nasal stuffiness and blockage. The results are purely palliative, and symptoms return with discontinuance of the drug. They do not immunize the patient and protect him from the effects of an allergic reaction for any prolonged period. Beyond that, the effects are often very disappointing, especially in severe cases. He felt that while it is evident that we will get better antihistaminic drugs as regards potency and toxicity, it is also evident that it would be preferable to attack the problem in a more fundamental way, at the beginning, rather than by neutralizing the end products of the allergen-antibody reaction. Some of the results of his experiences with various drugs follow. With Benadryl good results were obtained in 45 per cent of the patients, appreciable relief in 12 per cent, and no relief in 35.5 per cent. With Histadyl good relief was obtained in 31.8 per cent, appreciable relief in 36.4 per cent, and no relief in 31.8 per cent. The results with Pyribenzamine were quite similar, 40 per cent obtaining good relief, 29.1 per cent obtaining appreciable relief, and 30.9 per cent failing to obtain any relief. Using placebos he found that 5 per cent reported good relief, another 5 per cent appreciable relief, and 90 per cent no relief. On the other hand, his results with hyposensiti-

zation therapy alone were 56.6 per cent of the patients getting good relief, 29.6 per cent getting appreciable relief, and 14.8 per cent receiving no relief. When he used specific injection therapy plus histamine antagonists, his results were even better, with 82.4 per cent of the patients obtaining good results, 10.2 per cent of them appreciable relief, and only 7.4 per cent being failures.

In commenting on the use of antihistaminic drugs in allergic conditions, Schild[160] felt that we now possess drugs with extremely powerful antihistaminic activity (except for gastric secretion) and in some cases with remarkable activity against anaphylactic response. It is probable, however, that the two actions do not run strictly parallel. Furthermore, it is doubtful whether the anaphylactic reaction in animals can be wholly equated with human allergic reactions. It follows that antihistamines, like all drugs, cannot be completely assessed by animal work. The eventual appraisal of each individual drug can be made only by assessing it in patients exhibiting the disturbance against which the drug is to be used. Arner[5] is of the opinion that specific desensitization is superior to treatment with antihistaminic preparations alone, but that these drugs afford relief in cases with residual symptoms after specific treatment. The effect of antihistaminic therapy during specific desensitization was inferior to that of epinephrine; the use of antihistamine during specific desensitization did not seem to hasten desensitization. Although it is not within the province of this paper to delve into the pharmacology of the histamine antagonists, a few are here mentioned to indicate that work proceeds in this field in attempts to develop one of outstanding effectiveness. Wright[209] reported on four new Indole and three new Carbazole derivatives showing antihistaminic activity. Lands and Hoppe[103] examined the properties of three new antihistamines designated WIN 2848 (Thenfadil), WIN 2875, and WIN 2876. Of these the former was the most highly active antagonist and the data presented suggests that this drug may be a useful agent in the treatment of allergies. Sperber[181] et al reported on the synthesis of a series of pyridyl-substituted alkaminic ethers showing a high order of antihistaminic activity. Four new compounds were synthesized by Campaigne and LeSuer[31] for testing for antihistaminic activity and numerous other investigators are constantly synthesizing and testing various drugs for their antihistaminic activities. Some experimental studies in guinea pigs by Traina[189] suggest that folic acid protected them against anaphylaxis, and he further suggests that its action in anemia may be as an antihistamine.

An interesting study was conducted by Brewster and Dick[23] as to the antibacterial activity of Benadryl, Neo-Antergan, Thenylene and Pyribenzamine. Of these preparations only Benadryl was found to have very low bacteriostatic activity. Had these drugs been shown to have had such activity, they might have served to prevent the infectious complications that we not infrequently see in the post-hay fever season.

Maietta,[114] by integrating hyposensitization therapy and antihistamines, felt that he enabled forty-five pollen-sensitive patients to tolerate safely massive doses of pollen antigen. By this method they attained a large total pollen dosage and the optimum single dose level within a relatively short time, and with a substantial decrease in the number of required injections. He felt that the large pollen dosage so obtained conferred a degree of protection heretofore not always obtainable.

Using a standardized method of histamine iontophoresis Perry and Hearin[133] determined the duration of the "histamine blocking" activity of various antihistamines. By oral administration in single doses, the average maximum antihistaminic activity was obtained two hours after ingestion in the majority of patients—some showed this peak at three hours. In practically all of the subjects, activity had disappeared in five hours.

In allergic conjunctivitis, either accompanying hay fever or not, Daily and Daily[44]

felt that the combination of Privine-Antistine eye drops was valuable and appreciated by these patients, who complain of photophobia, lacrimation and itching. They found that it produced a rapid decongestion of the conjunctiva, and could be used indefinitely.

A new antihistamine designated 194-B by the White Laboratories was studied by Bernstein and Feinberg,[14] who found it to be a good drug for clinical use, combining effectiveness with a low incidence of undesirable toxic symptoms. The best results were obtained by the hay fever patients, with 64 per cent of 148 such patients obtaining satisfactory and consistent relief. Toxic side reactions were few in incidence and mild in degree.

Sixty cases of hay fever were treated by Swartz and Leibowitz[167] with Thephorin; 76.7 per cent of them obtained symptomatic relief. Toxic side reactions occurred in 12.6 per cent of these patients. It was the authors' opinion that this preparation was an effective histamine antagonist of low toxicity. In a series of children studied by Levin and Moss,[108] Thephorin was found to be effective in 81 per cent of those with hay fever. In their total series 8 per cent of the patients had reactions sufficiently severe to require discontinuance of the medication. Side reactions occurred in 20 per cent of the group, with the drug having a mild sedative effect instead of the stimulating effect seen in adults.

Phenergan was administered by Schulman[165] to twenty selected patients who were so-called failure cases, insofar as they derived little or no relief from other available antihistamines. These cases were not acute hay fever but perennial rhinitis, as he felt that generally mild to moderate seasonal rhinitis responds fairly well to such therapy. (However, this report is included here merely as a point of information concerning a not generally available histamine antagonist.) Phenergan was given once daily to these patients and nine of them complained of drowsiness, in one severe enough to necessitate discontinuance. Nine reported good results from the medication, and it was the authors' opinion that further study was warranted. Halpern[76] reported that experimental studies with this preparation have shown it to be a drug of unusual antihistaminic and antianaphylactic potency. Clinically, it was found to be of value in hay fever, serum sickness, urticaria, angioneurotic edema, and allergic purpura. Experimental studies indicate that this drug acts by decreasing capillary permeability. The only side effects were drowsiness and vertigo, which occurred in 25 per cent of the patients; these effects were impossible to predict and occurred even with very small doses. Vallery-Radot et al[190] reported that in 180 of 200 patients with hay fever, symptoms disappeared shortly following its administration in 25 to 50 mg doses. There were less favorable results in sixteen patients and no effects in four.

Pharmacologic studies in humans with a new piperazine compound, Perazil, by Jaros and Castillo[88] revealed a marked ability to inhibit the histamine-wheal response; a single oral dose imparted definite protection for over twenty-four hours; there was a very low incidence of toxic side effects. Jaros[87] treated twenty-three cases of hay fever with excellent results in twenty-two of them and moderate results in the remaining one. Only two patients in this group exhibited any side effects. He felt this drug to be a potent antihistamine exhibiting a prolonged activity of twenty-four hours. In a paper to be published shortly we have reported on a much larger series of patients, and though our results were not nearly as good as above, it was apparent that this preparation was a longer acting one albeit the duration of its action very rarely exceeded eight to ten hours.

Using Histadyl, Saletta[157] found that in ragweed hay fever excellent results were obtained only in those patients who had received preseasonal and coseasonal injections of allergenic extracts, and that untoward side reactions were negligible. Hartman[80] used an enteric-coated preparation of this drug on 107 patients who

obtained relief from the uncoated drug to see if the new preparation was effective. He found that symptoms were prevented in 89 per cent of these patients. The side reactions of nausea and epigastric distress were abolished in most of the patients in whom the uncoated drug produced this effect; however, the other usual side reactions were not diminished. A twenty-month-old patient of Snyderman's[180] accidentally ingested 800 mg of Thenylene with resultant cyanosis, unconsciousness and convulsions, which were followed by a period of cardiorespiratory depression. Supportive measures with a short-acting barbiturate was followed by improvement and complete recovery in twenty-four hours. Rives et al[152] reported that toxic symptoms developed in a sixteen-month-old girl two hours after the accidental ingestion of 100 mg of methapyrilene hydrochloride (Thenylene). The first manifestations were projectile vomiting and listlessness; symptoms of cerebral irritation soon developed. The CO_2 combining power of the blood fell to 25 mg per cent, and the non-protein nitrogen rose to 240 mg per cent; albumin and casts appeared in the urine. The temperature rose to 107° F. and death ensued after fifteen hours. Autopsy revealed cerebral edema and upper nephron nephrosis.

Eighty-four patients with hay fever, urticaria, and perennial allergic rhinitis were given Trimeton for clinical evaluation by Schiller and Lowell.[161] Satisfactory relief was obtained in fifty-five and partial relief in seventeen additional patients. Mild side reactions occurred in ten; the dosage ranged from 25 to 125 mg daily. The Committee on Therapy[148] of the American Academy of Allergy reported on the use of Trimeton in 3,068 patients. Seventy-seven investigators submitted their findings, and the committee after tabulating and analyzing them reached the following conclusions. This clinical study of Trimeton showed that this drug compared very favorably with the other histamine antagonists on the market in the alleviation of the symptoms of urticaria and of allergic rhinitis, especially pollen disease; also that it may produce fewer and less severe toxic symptoms than the older antihistamines.

Schulman and Fuchs[167] conducted clinical studies with iron as an adjunct to pollen immunization and antihistaminic therapy in hay fever. Their studies revealed comparable results obtained from pollen therapy with Trimeton alone and with pollen treatment, and Trimeton plus iron therapy; they indicated that iron has no therapeutic value in hay fever nor does it enhance the action of antihistamines.

Criep and Aaron[41] feel that Neohetramine is a potent antihistaminic drug and that the therapeutic results obtained from the use of this drug, in the symptomatic treatment of allergic disorders in infants and children of all ages, compares favorably with those obtained from other histamine antagonists. Undoubtedly some children will be relieved by one antihistaminic drug and others by a different drug. The side reactions obtained from Neohetramine were definitely lower than those observed from the use of other drugs, and therefore its use is safer in children. No serious side reactions or fatalities have been reported.

Schwartz and Reicher[172] treated a total of 111 patients with various allergic complaints, of which fifty-three were hay fever patients. All of these received preseasonal hyposensitization, and only those who had not received complete relief from symptoms were given Neohetramine. Symptomatic relief occurred in thirty-eight of these cases. Side reactions occurred in only 7.2 per cent of the total of 111 patients to whom the drug was administered. The Council on Pharmacy and Chemistry[89] of the AMA felt that the therapeutic action of Neohetramine is qualitatively the same as with other members of the antihistaminic series, but the frequency and degree of effectiveness is of a lower order. Its outstanding advantage is that it is tolerated better than the other compounds, sedation being less frequent and less severe.

Forty seasonal hay fever patients were treated with Chlor-Trimeton by Vickers and Barrett[192] who found the following. The optimum dosage was between six and 16

mg daily in divided doses. Ten patients received excellent results, eleven were markedly improved, sixteen had some improvement (the extent not being mentioned), and three received no benefit. Three patients exhibited toxic symptoms necessitating discontinuance. Allison and Robinson[4] treated thirty-six patients with allergic syndromes with Chlor-Trimeton, five of which were seasonal hay fever, the drug being effective in all of them. We conducted a study with this drug and were under the distinct impression that its degree of effectiveness varied very little from that of its sister drug, Trimeton.

Numerous investigators used local application of antihistamines in the nose, hoping that more intimate contact of the histamine antagonist with the shock organ itself would result in better relief. Their evaluation of this method of therapy follows. Feinberg and Bernstein[57] felt that the results of the application of aerosolized Pyribenzamine (2 per cent) solution to the nose indicated that it was a useful adjunctive form of therapy in the treatment of selected cases of nasal allergy. These topical treatments were not employed routinely for the relief of seasonal hay fever, but were confined to those patients who either were not getting sufficient results from oral antihistaminic therapy or who could not tolerate the latter. It was used in the main for severe cases of nasal congestion and required repeated administration. Benefit was apparent in twenty-seven out of thirty-four patients with this type of nasal congestion. Topical applications of the histamine antagonist did not produce post-shrinkage congestion. Aaron[1] treated five cases of seasonal hay fever by iontophoresis of Pyribenzamine. All had previously received injection therapy and therapy with antihistaminic drugs with no benefit. With iontophoresis these patients obtained relief for one to four days. In each case rhinorrhea, sneezing, and other symptoms stopped. Two cases of perennial rhinitis also were benefited. It was his opinion that this method may be of value in the treatment of allergic rhinitis that does not respond to other forms of treatment. He used a concentration of 5 per cent Pyribenzamine with exposure for five minutes. It was also his feeling that perhaps stronger concentrations with longer exposures might give more prolonged relief.

Eighty-one patients with allergic rhinitis were treated with topical applications of buffered Pyribenzamine solution by Brem and Zonis,[22] and over 90 per cent obtained satisfactory or excellent results. A 0.5 per cent solution was used, as stronger solutions caused local discomfort. No serious local or general effects were noted. They found that topical therapy was effective when orally administered antihistaminic drugs could not be tolerated because of distressing side effects; the local effect was temporary and the usual allergic diagnostic and therapeutic measures are necessary. Schwartz and Leibowitz[170] presented the results of their clinical evaluation of the topical application of 0.5 per cent isotonic buffered solution of Pyribenzamine hydrochloride in seasonal and nonseasonal hay fever, and found that in a group of ninety-five patients complete or partial symptomatic relief occurred in forty-nine of fifty-nine or 83 per cent of cases of seasonal hay fever. Of thirty-six cases of nonseasonal hay fever twenty-seven or 75 per cent obtained the same degree of relief. None of these patients experienced any systemic toxic reactions. However, 40 per cent of them experienced slight burning sensations in the nose, with marked burning occurring in two patients, necessitating discontinuance of the medication. They felt that these results warranted the use of this drug for topical application in seasonal and nonseasonal hay fever.

Zeller[211] felt that a 1 per cent solution of Pyribenzamine used as nose drops provided effective relief of hay fever, without objectionable side effects; further, that its action, used in this manner, was more rapid and offered more complete relief of symptoms than did the oral preparation. Frankly, our own experience with various topical antihistamines (Pyribenzamine, Antistine, Histadyl) has been very dis-

appointing in the type of cases where we felt its indication most important: namely, the "tightly-shut" severely-congested noses. In the milder types of cases we have not felt that topical applications were either needed or desirable.

Zolov[213] clinically evaluated Pyrrolazote in forty patients with hay fever and felt that a comparison with other histamine antagonists revealed that it was not as efficacious in the majority of the patients. As is generally the case, several patients who could not tolerate other antihistamines did obtain excellent relief with this drug. Of forty hay fever patients to whom the drug was administered, thirteen had excellent, eighteen good and nine no relief of symptoms. The incidence of side effects was twenty-four cases of a total of eighty-eight patients with various allergic complaints. Zolov[212] treated four cases of ragweed hay fever with small doses of intravenous Benadryl. The use of the drug was not consistently effective in any one of the patients so treated. Two of these patients showed excellent improvement, with some improvement occurring in the third and no improvement in the fourth case.

McGavack[118] in a general paper on the clinical application of Benadryl concludes that it seems quite clear that this drug has found a definite place in the treatment of allergic diseases. In the case of Benadryl, in addition to its predominant ability to block quantitatively the action of histamine in the tissues, there is a second weaker hyoscine-like action which enhances the value of the drug where a mild sedative as well as antihistaminic effect is desirable. He felt that no one drug will surpass all others in therapeutic applicability to all allergic diseases, but that one may serve a better purpose in one instance, another in a second, and still another in a third. A report on the absence of effects of Benadryl on the hematopoietic system was made by Leopold,[104] who found that this drug administered to patients for periods ranging from six to seventeen months, did not produce any pathologic alteration in the hemoglobin, red cell, total white cells, or neutrophil content of the blood. No manifestations of purpura or hemorrhage occurred.

Schulman and Fuchs[166] reported on their clinical experiences with B-(p-methylbenzhydryloxy)-ethyldimethylamine hydrochloride, a compound chemically and pharmacologically closely related to Benadryl. It was administered to 135 patients with varied allergic manifestations. Eighty-seven per cent of those with seasonal allergic rhinitis were relieved, 21 per cent being completely relieved and 66 per cent partially, though satisfactorily relieved. Side effects occurred in 15 per cent of all the cases, and only two patients could not tolerate the drug. They felt that this preparation was a potent adjuvant for relieving allergic symptoms when used with the usual therapeutic procedures such as elimination of allergens and hyposensitization.

Our conclusions of last year,[96] on the use of antihistamines, have not been altered by any of the subsequent work in the field. All of these drugs are only palliatives, suitable only for symptomatic relief. When they are discontinued symptoms return if the conditions leading to the allergic state have not been altered. The physician must still make attempts to recognize the offending allergens and to eliminate them if possible, or to hyposensitize the patients to them. These drugs have a place "in conjunction" with orthodox therapy when the latter does not adequately control the symptoms, or before that therapy brings relief to the patient.

MISCELLANEOUS

Miller[124] reported on the effect of long-continued respiratory allergy to dental occlusion. He found no relation to the disease or any progress during therapy. This report is contrary to our clinical observations.

Bordley et al[19] and Canback[32] report on ACTH and Cortisone. Bordley[19] found diminution of nasal polyps, tissue changes in the nasal mucosa, and little or no changes in the skin tests while the patients were under therapy.

Ingelstedt and Ivstam[86] studied the possible spread of intravenously deposited fluorescein in the nasal secretion in hay fever patients under conditions of infection, allergy, and experimentally induced conditions. In acute infectious and allergic conditions, bright fluorescence of nasal secretion was noted. Chronic conditions cause no fluorescence. It is thought by these investigators that nasal secretion in the acute and infectious stage is an exudation and a product of the mucous membrane glands alone. If 1:1000 histamine is injected it causes no fluorescence. When the mucous shield is removed from the nasal tissues, fluorescence occurs. Iontophoresis on the wiped surface developed good fluorescence. When premedicated with an antihistamine, iontophoresis with histamine was without effect.

Another study of similar nature by Criep and Levine[42] was reported in which the skin was used. The dermofluorometer was used in observing fluorescence. Little changes between normal and allergic skins were noted.

A number of articles dealing with allergy were reported. Those by Ratner,[145] McQuire,[112] King,[98] Grove,[75] and Bullen[29] are worth mentioning.

At the annual convention of the American Medical Association, a session on allergy[93] was presented by Ratner & Swineford, Piness, Lee, and Webster.

A gift of $10,000[120] has been presented by the Asthmatic Children's Aid to the University of Illinois Allergy Clinic to establish a histochemical laboratory for experiments in allergy. Asthmatic Children's Aid was organized in 1940 to further research on asthma and allergy and to provide relief for underprivileged children. The organization contributes also for the care of patients in clinics and the education of doctors who will specialize in the treatment of allergic diseases. The association has contributed a total of $50,000 to the University of Illinois in support of the Allergy Clinic. They have also contributed sums of money for the maintenance of allergy clinics in the city of Chicago.

PSYCHODYNAMICS

There is ample evidence in the recent literature that psychodynamic factors have a definite relationship to allergic syndromes.

Stevenson and Wolff[185] discuss the relationship of life situations, emotions, and the production of bronchial mucus.

Salen[156] stresses that psychogenic factors are secondary to allergenic factors.

A number of other investigators have written excellent discussions on this problem. Among them are Abramson,[214] Shure,[178] Nexmand,[128] Ascher,[9] Stalker,[184] and Metzger.[123]

Cohen and Abram[35] studied the emotional components in allergy from the statistical point of view. The method used to evaluate personality was the Cornell Index. The study proved that practically all allergic conditions are more common in males than in females from birth to fifteen years, and more common in females than in males from fifteen to forty-five years of age. Emotional disturbances which precipitate attacks are found more frequently in women than in men between the ages of twenty and forty. This confirms the reports of Nelson and Bray.

REVIEWS

Many reviews dealing with some facet of clinical hay fever have appeared in the literature this year. Gill,[72] Taub,[187] and Woods[208] have excellent articles from the standpoint of the eye and its adnexa. Schlitter,[164] Squier,[182] and Craddock[39] report on this subject from the otolaryngological point of view. Cortes,[37] Glaser,[71] Rodriguez,[37] and McGee[119] review the pediatric point of view with excellent discussions on pollenosis. An excellent review in Spanish is that of Toulet.[188] Among the other general reviews are those of Clark,[34] Claman,[33] Criep,[40] Figley,[62] Feinberg,[56] Wolf,[207] Edwards,[54] Simon,[179] and Wittich.[204]

PROGRESS IN ALLERGY

BOOKS

A number of books have been added to the ever-increasing library on allergy. Tuft's[220] *Clinical Allergy,* second edition, is, as ever, concise, easy to read, accurate. Grafton Tyler Brown's[215] book, *Pollen-Slide Studies,* fills a need for those who are not familiar with accurate drawings, photographs, and descriptions of important hay-fever-producing pollens and larger fungus spores, but it is not complete and hardly worthwhile as a reference book. It would be well for all to read as reference books Abramson's[214] *Psychodynamics and the Allergic Patient* and Hansel's[217] *Allergy in Relation to Otolaryngology.* Both books have an outstanding group of contributors. They stress the relation of psychodynamics and otolaryngology to allergy. Many important points referable to hay fever can be gleaned from reading them.

Two excellent books have appeared from across the seas: *Progress in Allergy* edited by Paul Kallos,[218] and *Allergie* edited by Pasteur Vallery-Radot.[221] It is not surprising that in both books the majority of the contributors are Americans. Kabat's[218] chapter on Immunochemistry in the *Progress in Allergy* is excellent.

A book for the layman written by Swartz,[219] *Allergy—What It Is and What To Do About It,* has been well received.

Current Therapy, edited by Conn,[216] has a group of contributors who are authorities in their particular subject, and it is worth reading.

REFERENCES

1. Aaron, T. H.: Iontophoresis of Pyribenzamine in allergic rhinitis. Canad. M. A. J., 61:301-3, (Sept.) 1949.
2. Abram, Lewis E.: An evaluation of conjunctival testing in extrinsic respiratory allergy. J. Allergy, 20:65-70, 1949.
3. Abramson, Harold: Psychodynamics and the allergic patient. J.A.M.A., 141: 280, (Sept.) 1949.
4. Allison, J. R., and Robinson, A. M.: J. South Carolina M. A., 43:344, 1949.
5. Arner, B.: Antihistamine treatment in allergic diseases. Nord. Med., 39:1375-1410, (July) 1948.
6. Arner, B.: Antihistamine treatment in allergic diseases. Nord. Med., 39:1386, 1948.
7. Arner, B.: Experiments in induction of allergy by inhalation of allergen. Nord. Med., 42:1255-1286, (July) 1949.
8. Arner, B.: Experiments in provocation of allergy by inhalation of allergens. Nord. Med., 42:1257-1264, 1949.
9. Ascher, E.: Psychosomatic medicine; a critique. J. South Carolina M. A., 45:113-6, (April) 1949.
10. Ashley, R. E.: Dust therapy in allergy of the ear, nose and throat. Ann. Otol., Rhin. & Laryng., 58:417-28, (June) 1949.
11. Bain, W. A.: The quantitative comparison of histamine antagonists in man. Proc. Roy. Soc. Med., 42:615-23, (Aug.) 1949.
12. Beakey, John F.; Bresnik, E.; Levinson, L., and Segal, M. S.: Evaluation of therapeutic substances employed for the relief of bronchospasm. Ann. Allergy, 7:113-122, 1949.
13. Becker, E. L., and Munoz, J.: Multiplicity of antigens in ragweed pollen extracts as demonstrated by the technic of Oudin. Proc. Soc. Exper. Biol. & Med., 72:287-9, (Nov.) 1949.
14. Bernstein, T. B., and Feinberg, S. M.: Histamine antagonists; and experimental and clinical study of N, N-dimethyl-N'-2 thiazolyl-N'-p-methoxybenzyl-ethylenediamine hydrochloride. J. Lab. & Clin. Med., 34:1007-9, (July) 1949.
15. Bernton, H. S.: A review of the chemical approach to allergens. Ann. Allergy, 7:13-31, (Jan.-Feb.) 1949.
16. Bieberdorf, F. W., and Argabrite, John W.: Extracts of molds grown on synthetic media. J. Allergy, 20:50-56, 1949.
17. Blanton, W. B., and Sutphin, A. K.: Death during skin testing. Am. J. M. Sc., 217:169-173, (Feb.) 1949.
18. Blumenthal, J. S.: The antihistamine drugs in the treatment of hay fever in the adult. J. Lancet, 69:215-219, (June) 1949.
19. Bordley, J. E.; Carey, R. A., et al: Preliminary observations on the effect of

adrenocorticotropic hormone in allergic diseases. Bull. Johns Hopkins Hosp., 85:396-8, (Nov.), 1949.
20. Boure, G. H.: Vitamin C and immunity. Brit. J. Nutrition, 2:341-7, 1949.
21. Brandberg, O., and Wilander, O.: The testing and desensitizing of allergic children. Acta Allergol., 2:51-56, 1949.
22. Brem, Jacob, and Zonis, Jonathan: Intranasal application of buffered tripelennamine (Pyribenzamine) solution in allergic rhinitis. J. Allergy, 20:70-73, 1949.
23. Brewster, J. M., and Dick, L. A.: The antibacterial activity of some of the common antihistamine drugs. Texas Rep. Biol. & Med., 7:69-72, (Spring) 1949.
24. Brewster, J. M.: Antihistaminic drugs in the therapy of the common cold. U. S. Nav. M. Bull., 49:1-11, (Jan.-Feb.) 1949.
25. Brown, Ethan Allan, and Ruskin, Simon L.: The use of cevitamic acid in the symptomatic and co-seasonal treatment of pollenosis. Ann. Allergy, 7:65-71, 1949.
26. Brown, J. R.: The antibiotic properties of the common ragweed. Texas Rep. Biol. & Med., 7:3-11, (Spring) 1949.
27. Bruun, E.: Control examination of the specificity of specific desensitization in asthma. Acta Allergol., 2:122-128, 1949.
28. Budd, E., and Freeman, J.: Allergic specificity of pollens. Lancet, 2:1171, (Dec. 24) 1949.
29. Bullen, Stearns: What should the general practitioner do about allergy? J.A.M.A., 140:13, (May) 1949.
30. Bukantz, S. C.; Johnson, M. C.; and Hampton, S.: Quantitative immunologic studies with allergens. Colorimetric absolute methods in the analysis of factors influencing precipitation of ragweed pollen extracts and homologous rabbit antisera. J. Allergy, 20:1-17, (Jan.) 1949.
31. Campaigne, E., and LeSuer, W. M.: Three substituted thiopenes; antihistaminics of the N-(3-thenyl-) ethylenediamine series. J. Am. Chem. Soc., 71:333-5, (Jan.) 1949.
32. Canback, T.: ACTH and cortisone. Farm. Rev., 48:533-7, (Sept.) 1949.
33. Claman, L. N.; Cassirer, A. M., et al: The allergic patient. J. Am. M. Women's A., 4:225-30, (June) 1949.
34. Clark, N. S.: Allergy in general practice. North Carolina M. J., 10:580-584, (Nov.) 1949.
35. Cohen, Milton, and Abram, Lewis F.: A statistical study of the emotional component in allergy; its relationship to the age and sex distribution of 5,583 patients. J. Allergy, 20:207-210, 1949.
36. Cooke, R. A.: The allergy factor in disease. Ann. Int. Med., 31:17-32, (July) 1949.
37. Cortes, J. L., and Rodriguez, H. E.: Alergia en ninos. Medicina, 29:121-6, (April) 1949.
38. Coulson, E. J.; Spies, J. R., and Stevens, H.: The immunochemistry of allergens; the relationship of carbohydrate to the antigenic properties of the allergenic protein from cottonseed. J. Immunol., 62:171-182, (June) 1949.
39. Craddock, W. H.: Perennial nasal allergy; a review of 80 cases. Ann. Otol., Rhin. & Laryng., 58:671-99, (Sept.) 1949.
40. Criep, L. H.: Allergy in general practice. Am. Pract., 4:131-134, (Nov.) 1949.
41. Criep, L. H., and Aaron, T.: Antihistaminic drugs in pediatric allergy. J. Pediat., 34:414-20, (April) 1949.
42. Criep, L. H., and Levine, M. I.: Studies of capillary permeability in allergy with the dermofluorometer. J. Allergy, 20:185-198, 1949.
43. Curry, J. J.; Fuchs, J. E., and Leard, S. E.: Clinical and experimental studies with Orthoxine in the treatment of bronchial asthma. J. Allergy, 20:104-10, (March) 1949.
44. Daily, R. K., and Daily, L., Jr.: Use of Privine-Antistine drops in ophthalmology. Am. J. Ophth., 32:441, (March) 1949.
45. Dammin, G. J., Bukantz, S. C.: Modification of biologic response in experimental hypersensitivity. J.A.M.A., 139:358, (Feb.) 1949.
46. De Castro, H. C.: Factores etiologicos das doencas allergicas (Etiological factors of allergic diseases). O Hospital. Rio de Janeiro, 35:549-573, Table 3, 1949.
47. Dickstein, Bernard: The effect of substitution of Antistine (Phenyl-benzyl-amino-methyl-imidazoline) for Benadryl or Pyribenzamine during the height of the ragweed pollen season. Ann. Allergy, 7:250-254, 1949.

48. Dilks, E., and Wolfe, H. R.: The effect of Seitz filtration of the protein content and precipitin reaction of diluted antigen solutions. Physiol. Zool., 22: 22-30, (Jan.) 1949.
49. Doyle, Gerald: Nasal desensitization in allergy. Med. J. Australia, 35:94-97, 1948. Bio. Ast., 23:26, (June-July) 1949.
50. Dumm, J. Federico, and Zarate, O.: Anthemis cotula as a cause of pollen allergy. Alergia, 3:64-69, (July-Oct.) 1949.
51. Dunlop, D. M.: The antihistamine drugs. J. Pharm., 1:1-10, (Jan.) 1949.
52. Durham, O. C.: Airborne allergens in the national parks. J. Allergy, 20: 255-269, (July) 1949.
53. Dutton, L. O.: Mold fungi in the etiology of respiratory allergic diseases; intrinsic fungus factors in relation to asthma. Ann. Allergy, 7:585-91, (Sept.-Oct.) 1949.
54. Edwards, H. E.: Aspects of perennial allergic rhinitis and asthma in childhood. Canad. M. J., 61:36-8, (July) 1949.
55. Eggston, Andrew A.: Manhattan Eye, Ear and Throat Hospital. Allergy. New York State J. Med., 49:539-542, 1949.
56. Feinberg, S. M.: Asthma; present status of therapy. Bull. Chicago M. Soc., 51:1062-6, (June) 1949.
57. Feinberg, S. M., and Bernstein, T. B.: Nebulized Pyribenzamine in nasal and bronchial allergy. J. Lab. & Clin. Med., 34:1078-80, (Aug.) 1949.
58. Feinblatt, H. M., and Ferguson, E. A.: Hydrolyzed oral hay fever antigens. J. Med., 48:2720-2723, (Dec.) 1948.
59. Feinblatt, T., and Love, R.: Oral pollen absorption. Ann. Allergy, 7:228-231, 1949.
60. Feinblatt, T., and Love, R.: Oral pollen absorption. J.A.M.A., 141:54, (Sept.) 1949.
61. Fenton, M. M., and Huffman, E. R.: Iontophoresis of Pyribenzamine hydrochloride in nasal allergy. J. Allergy, 20:75-76, 1949.
62. Figley, K. D.: Some unanswered questions in clinical allergy. Canad. M. J., 61:24-7, (July) 1949.
63. Figley, K. D., and Rawling, F. A.: Mold fungi in the etiology of respiratory allergic diseases; the use of a concentrated extract in the treatment of mold-sensitive patients. Ann. Allergy, 7:5, (Sept.-Oct.) 1949.
64. Fitzgerald, J. D. L., and Sherman, W. B.: The specificity of blocking antibody induced by grass pollen extracts. J. Allergy, 20:286-91, (July) 1949.
65. Foreign Letters (Oslo): An asthma survey. J.A.M.A., 139:953-4, (April) 1949.
66. Foreign Letters (Paris) Congress of Allergy. J.A.M.A., 141:1317, (Dec.) 1949.
67. Frankland, A. W.: Hay fever. Med. Illust., 3:193-7, (May) 1949.
68. Franklin, W., and Lowell, F.: Failure of ragweed pollen extracts to destroy white cells from ragweed sensitive patients. J. Allergy, 20:375-377, 1949.
69. Friedlaender, A. S., and Friedlaender, S.: Correlation of experimental data with clinical behavior of synthetic antihistaminic drugs. Ann. Allergy, 7:83-90, (Jan.-Feb.) 1949.
70. Friedlaender, S., and Friedlaender, A. S.: Antihistamine therapy in allergy. J. Lancet, 69:220-223, (June) 1949.
71. Glaser, Jerome: Progress in pediatric allergy. Ann. Allergy, 7:268-295, 1949.
72. Gill, W. D.: Ocular allergy. Allergic phenomena affecting eye and its adnexa. Arch. Ophth., 42:238-248, (Sept.) 1949.
73. Greco, J. B.: Fundamentals of allergic diseases. Rio de Janeiro, 35:731-744, 1949.
74. Grinnell, E.: The diagnosis and treatment of mold allergy. J. Lancet, 69: 205-208, (June) 1949.
75. Grove, R. C.: The importance of sinusitis in allergic manifestations. Laryngoscope, 84:82-91, (Jan.-Mar.) 1949.
76. Halpern, B. N.: Recent advances in the domain of antihistaminic substances: the phenothiazine derivatives. Bull. New York Acad. Med., 25:323, 1949.
77. Hampton, S. F., and Johnson, M. C.: Quantitative immunologic studies with allergens. J. Allergy, 20:19-31, (Jan.) 1949.
78. Harkavy, Joseph: Allergic factors in gout. J.A.M.A., 139:80, (Jan.) 1949.
79. Harris, Hilbert: Therapeutic effects of certain antihistamine drugs in allergic conditions. Ann. Allergy, 7:206-215, 1949.
80. Hartman, Milton M.: Possible uses of a delayed action antihistaminic. Clinical trials. Ann. Allergy, 7:679-80, (Sept.-Oct.) 1949.

81. Haurowitz, F.: Biological problems and immunochemistry. Quart. Rev. Biol., 24:101, (June) 1949.
82. Heise, Herman A.: Symptoms of hay fever caused by algae. J. Allergy, 20: 383-5, (Sept.) 1949.
83. Heise, Herman, and Heise, Eugenia: The influence of temperature variations and winds aloft on the distribution of pollens and molds in the upper atmosphere. J. Allergy, 20:378-382, (Sept.) 1949.
84. Howell, F. C.; Curry, J. J., and Schiller, I. W.: New England J. Med., 240:45-51, (Jan.) 1949.
85. Hyde, H. A.: Phenology of British hay fever plants and its significance to allergists. Brit. M. J., 1:895-7, (May) 1949.
86. Ingelstedt, S., and Ivstam, B.: Hay fever, source of nasal secretion in infectious allergic experimental conditions. Acta otolaryng., 37:451-5, 1949.
87. Jaros, S. H.: The clinical application of a new piperazine compound; clinical observations. Ann. Allergy, 7:466-70, (July-Aug.) 1949.
88. Jaros, S. H.; Castillo, J. C., and DeBeer, E. J.: The clinical application of a new piperazine compound. Ann. Allergy, 7:458-465, (July-Aug.) 1949.
89. JA.M.A.: Council on Pharmacy and Chemistry. 139:1148-9, (April 23) 1949.
90. J.A.M.A.: Council on Pharmacy and Chemistry. Antihistaminic preparations. 130:378, (Feb. 5) 1949.
91. J.A.M.A.: Council on Pharmacy and Chemistry. Too many drugs. 139:378, (Feb. 5) 1949.
92. J.A.M.A.: Ragweed in Honolulu. 139:272, 1949.
93. J.A.M.A.: Session on Allergy. 139:1178, (April 23) 1949.
94. Kabat, Elvin A.: Immunochemistry. Progress in Allergy, pp. 11-51, 1949.
95. Kaplan, Leo: A survey of air-borne fungi of the Boston area in relation to inhalant allergy. Am. J. Botany, 36:810, 1949.
96. Kaplan, Morris A., and Ehrlich, Norman J.: Hay fever. Ann. Allergy, 7:689-718, (Sept.-Oct.) 1949.
97. Keeney, Edmund L., and Eriksen, Nils: The chemical isolation and biologic assay of extracellular antigenic fractions from pathogenic fungi. J. Allergy, 20:172-185, 1949.
98. King, P. F.: Some manifestations of nasal allergy: a survey of 150 cases in the Middle East. J. Laryng. & Otol., 63:501-10, (Sept.) 1949.
99. Kleinman, Irwin A.: An adapter for the rapid performance of the puncture skin test. Ann. Allergy, 7:372-377, 1949.
100. Krasno, L. R.; Grossman, M. I., and Ivy, A. C.: The inhalation of 1-(2',4'-dihydroxyphenyl)-2-isopropylaminoethanol (norisodrine sulfate dust). J. Allergy, 20:111-116, 1949.
101. Kugelmass, I. N.: Antihistaminic therapy of allergic disorders in infants and children. New York State J. Med., 49:2313-8, (Oct.) 1949.
102. Lachaux, M.: Les antihistaminiques de synthese, au point de vue chimique et pharmacodynamique. Rev. Med. de la Suisse Rom., 69:255-269, (April) 1949.
103. Lands, A. M.; Hoppe, J. C., et al: The pharmacological properties of three new antihistaminic drugs. J. Pharmacol. & Exper. Therap., 95:45-52, (Jan.) 1949.
104. Lazarowitz, L. C.: Hay fever as a public health problem. New York State J. Med., 49:1960-2, (Aug.) 1949.
105. Leopold, Howard C.: The absence of the effects of Benadryl on the hematopoietic system. Ann. Allergy, 7:510-12, (July-Aug.) 1949.
106. Leopold, Howard C.: Summer asthma mysteries. J. Allergy, 20:84, (Jan.) 1949.
107. Levin, R.: The role of fungi in inhalant allergy. Am. J. M. Technol., 2:5, (Jan.) 1949.
108. Levin, Samuel, and Moss, S. S.: Thephorin in allergic children. J. Pediat., 36:616-20, (May) 1949.
109. Lipman, William H.: The treatment of bronchial asthma with Isuprel. Ann. Allergy, 7:384-390, 1949.
110. Loveless, M. H., and Dworin, M.: Allergy and antihistamine therapy. A review. Bull. New York Acad. Med., 25:473-87, (Aug.) 1949.
111. Loveless, M. H., and Dworin, M.: Six histamine antagonists in hay fever, with a review of the literature. J. Am. M. Women's A., 4:105-11, (Mar.) 1949.
112. Maguire, C. C.: General allergies in children. J. Florida M. A., 36:287-90, (Nov.) 1949.

113. Maietta, A. L.: The diagnosis and treatment of perennial allergic coryza. Ann. Allergy, 7:359-366, 1949.
114. Maietta, A. L.: Hay fever therapy—unusually good results in pollinosis with combined antigen-antihistamine therapy shortening treatment of hay fever. Ann. Allergy, 7:789-798, (Nov.-Dec.) 1949.
115. Maietta, A. L.: Letters International Correspondence Club of Allergy, 12:75, 1949.
116. Manche, R., and Orzechowski, G.: Clinical application of the sensitization of peripheral sympathetic end-organs. Experimentelle Pathologie and Pharmakologie, 205:311-321, 1948.
117. Marchand, Angel M.: Plantas polinosigenicas de Puerto Rico. Alergia, 111: 122, (Nov.-Feb.) 1948-1949.
118. McGavack, Thomas H.: The nature of Benadryl activity and its clinical application. Ann. Allergy, 7.232-240, 1949.
119. McGee, W. Ambrose: Pediatric allergy. Wisconsin M. J., 48:229-231, 1949.
120. Medical News: gift for laboratory to study allergy. J.A.M.A., 140:967, (July 16) 1949.
121. Medical News: survey of allergy-producing molds. J.A.M.A., 140-339, (May 21) 1949.
122. Meier, Von R., and Buche, K.: Pharmakologie der Antihistaminica. Progress in Allergy, pp. 290-295, 1949.
123. Metzger, F. C.: Allergy and psychoneuroses. J. Nerv. & Ment. Dis., 109: 240-5, (Mar.) 1949.
124. Miller, H. I.: The relation of long-continued respiratory allergy to occlusion. Am. J. Orthodontics, 35:789-90, (Oct.) 1949.
125. Mitroni, M.: Clinical evaluation of modern skin test for allergy. Rev. med. cubana, 60:221-246, (April) 1949.
126. Nevius, William B.: Management of the child with hay fever and asthma. J. M. Soc. New Jersey, 46:17-22, 1949.
127. Newland, John E.: A dye incorporating rapid permanent pollen mounting method. J. Allergy, 20:396-397, (Sept.) 1949.
128. Nexmand, P. H.: Clinical studies of Besnier's prurigo. J.A.M.A., 42:448, (Feb. 11) 1950.
129. Nilsby, Ivar: Allergy to moulds in Sweden (a botanical and clinical study). Acta Allergol., 2:57-90, 1949.
130. Pady, S. M., and Kelly, C. D.: Use of Silicones in aerobiology. Science, 110:187, 1949.
131. Passarelli, N.; DeMaranda, M. P., and De Castro, D.: A study of the incidence of air-borne fungi in the city of Rio de Janeiro. Ann. Allergy, 7:334-8, (May-June) 1949.
132. Paterson, G. R.: The antihistaminics. Canad. Pharm. J., 82:69-71, (Jan. 15) 1949.
133. Perry, D. J., and Hearin, D. L.: Antihistaminic activity of orally administered compounds. J. Invest. Dermat., 13:29-34, 1949.
134. Prince, Homer E.: Mold fungi in the etiology of respiratory diseases; further studies with mold extracts. Ann. Allergy, 7:301-306, 1949.
135. Prince, H. E., and Arbesman, C. E.: Mold fungi in the etiology of respiratory allergic diseases; further studies with mold extracts. Ann. Allergy, 7:597-609, (Sept.-Oct.) 1949.
136. Pollens, California: Allergy and myopia. Queries and Minor Notes. J.A.M.A., 139:554, 1949.
137. Problems: Antihistaminic drugs. Queries and Minor Notes. J.A.M.A., 139: 420, 1949.
138. Queries and Minor Notes: ACTH in treatment of asthma. J.A.M.A., 142:1328, (April) 1950.
139. Queries and Minor Notes: Discomfort following bowel movements. J.A.M.A., 141:236, (Sept. 17) 1949.
140. Queries and Minor Notes. McClintock, R. S., Mold sensitivity. J.A.M.A., 139: 1303, (April 30) 1949.
141. Queries and Minor Notes: Mold sensitivity in boy two and half years. J.A.M.A., 139:1303, (April 30) 1949.
142. Queries and Minor Notes: Vasomotor rhinitis in autumn. J.A.M.A., 142:1116, (April 8) 1950.
143. Raika, O.: Theoretical basis of allergy. Orvosok Lapja, 5:592-603, (Aug. 28) 1949.

144. Rappaport, Ben Z., and Becker, Elmer L.: Quantitative studies in skin testing. J. Allergy, 20:5, (Sept.) 1949.
145. Ratner, Bret: Asthma in children. New Med., 5:17-43, 1949.
146. Rees, H. F., and Ward, B. B.: Fatal reaction to methapyriline (Thenylene). J.A.M.A., 140:1022-23, (July 25) 1949.
147. Reimann, Hobart A.: Periodic diseases. J.A.M.A., 141:175, (Sept. 17) 1949.
148. Report of the Committee on Therapy. J. Allergy, 20:310,(July) 1949.
149. Rinkel, Herbert: Inhalant allergy. The coseasonal application of serial dilution testing. Factors modifying the whealing response of the skin. Ann. Allergy, 7:631-639, (Sept.-Oct.) 1949.
150. Rinkel, Herbert J.: Inhalant allergy. The coseasonal application of serial dilution testing (titration). Ann. Allergy, 7:639-645, (Sept.-Oct.) 1949.
151. Rinkel, Herbert J.: Inhalant allergy. The whealing response of the skin to serial dilution testing. Ann. Allergy, 7:625, (Sept.-Oct.) 1949.
152. Rives, H. F.; Ward, B. B., and Hicks, M. L.: A fatal reaction to methapyriline. J.A.M.A., 140:1022-4, (July 23) 1949.
153. Rose, B.; Pare, J. A. P.; Pump, K., and Stanford, R. L.: Preliminary report on adrenocorticotropic hormone (ACTH) in asthma. Canad. M. A. J., 62:6-9, (Jan.) 1950.
154. Russell, B.: Treatment of hay fever by injection of nasal mucosa with alcohol. Lancet, 1:1098, (June 25) 1949.
155. Sacks, S.: How far can wind-borne pollen be disseminated? J. Allergy, 20:453, (Nov.) 1949.
156. Salen, E. B.: Significance of psychogenic factors in allergic diseases. Nord. Med., 42:1687-90, 1949.
157. Saletta, S. N.: A new antihistaminic compound for the treatment of urticaria and hay fever. Ann. Allergy, 7:366, (May-June) 1949.
158. Schaffer, Nathan: Ann. Allergy Survey. J.A.M.A., 140:494, (June) 1949.
159. Schapiro, Mark M., and Sadove, Max: Oral procaine hydrochloride therapy in asthma. Ann. Allergy, 8:85, (Jan.-Feb.) 1950.
160. Schild, H. O.: The experimental evidence for the use of antihistamine drugs in allergic conditions. Proc. Roy. Soc., London, 42:623-5, (Aug.) 1949.
161. Schille, I. W., and Lowell, Francis C.: Trimeton, a new antihistaminic drug. New England J. Med., 240:215-16, 1949.
162. Schiller, I. W., and Lowell, F. C.: Orthoxine in bronchial asthma, a clinical evaluation. New England J. Med., 241:231-3, (Aug. 11) 1949.
163. Schiller, Irving W.; Lowell, F. C.; Franklin, W., and Denton, Clare: Orthoxine in bronchial asthma, a clinical evaluation. Quart. Rev. Allergy & App. Immunol., 3:209, (Dec.) 1949.
164. Schlittler, E.: Nature and sign of allergy role in otorhinolaryngology. Pract. oto-rhinolaryng., 11:249-276, 1949.
165. Schulman, M. H.: Phenergan (R.P. 3277). Preliminary report of clinical effectiveness. Ann. Allergy, 7:506-509, (July-Aug.) 1949.
166. Schulman, P. M., and Fuchs, A. M.: Clinical experiences with B-(p-methylbenzhydryloxy)-ethyldimethylamine hydrochloride, a new antihistaminic. Ann. Allergy, 7:502-5, (July-Aug.) 1949.
167. Schulman, Philip M., and Fuchs, Abner M.: Clinical studies with iron as adjunct to pollen immunization and antihistaminic therapy in hay fever. J. Allergy, 20:444-448, 1949.
168. Schutzbank, F. B.: Climatotherapy in allergic diseases. J.A.M.A., 139:1260, (April 30) 1949.
169. Schwartz, Emanuel: Comparative toxicity and side effects of the antihistaminic drugs. Ann. Allergy, 7:770, (Nov.-Dec.) 1949.
170. Schwartz, Emanuel, and Leibowitz, Harry: Local nasal therapy with Pyribenzamine in seasonal and nonseasonal hay fever. J. Allergy, 20:269-273, 1949.
171. Schwartz, E., and Leibowitz, Harry: Thephorin. A new antagonist in the symptomatic treatment of allergy. New York State J. Med., 49:533-34, 1949.
172. Schwartz, Emanuel, and Reicher, Jacob: A clinical evaluation of Neohetramine in allergic diseases. Ann. Allergy, 7:320-325, 1949.
173. Schwartz, E., and Wolf, J.: Histamine antagonists. J. Allergy, 20:32-49, 1949.
174. Schwarzmann, A.: Anti-allergic therapy with syn. haptena. Schweitz. med. Wchnschr., 79:498-502, (June 4) 1949.
175. Segal, M. S.: Hay fever therapy; symptomatic management of hay fever. Bull. New England M. Center, 11:97-106, (June) 1949.
176. Seltzer, Alvin: A handy dropper for scratch testing. Ann. Allergy, 7:522, (July) 1949.

177. Shulman, Maurice H.: The use of ragweed ointment in determining seasonal variation of ophthalmic sensitivity. J. Allergy, 20:83, (Jan.) 1949.
178. Shure, Norman: Psychosomatics. J.A.M.A., 140:834, (July 2) 1949.
179. Simon, Frank: Clinical allergy. J.A.M.A., 139:1258-9, 1949.
180. Snyderman, Harry S.: J. Pediat., 35-376-77, 1949.
181. Sperber, N.; Papa, D., et al: Pyridyl-substituted alkamine ethers as antihistaminic agents. J. Am. Chem. Soc., 71:887-90, (Mar.) 1949.
182. Squier, T. L.: Clinical allergy for nose, throat specialists. Wisconsin M. J., 48:598-600, (July) 1949.
183. Staffieri, M.: Acute allergic hyrodps of the middle ear caused by skin allergie tests. Quart. Rev. Allergy & App. Immunol., 3:90-91, (June-Sept.) 1949.
184. Stalker, H.: The psychosomatic diseases; a hypothetical formulation. J. Ment. Sc., 95:399, 355-368(April) 1949.
185. Stevenson, I. P., and Wolff, H. G.: Life situations, emotions, and bronchial mucus. Psychosom.Med., 11:223-7, (July-Aug.) 1949.
186. Strauss, M., and Spain, W. C.: A single apparatus for the defatting, drying, storage and extraction of many antigenic substances. J. Allergy, 20:301-306, (July) 1949.
187. Taub, S. J.; Fowler, M. J., et al: Allergic manifestations of the eye and surrounding structures. Am. Pract., 1:664-71, (July) 1949.
188. Toulet, J. P.: Therapeutic progress in allergy. Prensa med. argent., 36: 1276-1283, (July 8) 1949; 1339-1344, (July 15) 1949.
189. Traina, V.: Folic acid as an anti-anaphylactic. Nature, 163:364, (Mar. 5) 1949.
190. Vallery-Radot, P.; Blamoutier, P., and Halpern, B.: Presse med., 56:714, 1949.
191. Vargas, Plutarco Nararjo: Alergic a inhalantes en el Ecuador. Alergia, 2:61-63, (July-Oct.) 1949.
192. Vickers, M. A., and Barrett, R. J.: Clinical evaluation of a newer antihistaminic, Chlor-Trimeton. J. Maine M. A., 40:356, (Dec.) 1949.
193. Vieitez, Cortizo, Ernesto: Botanical studies on the allergy-producing flora. An. Inst. Esp. Edafologia, Ecol. y Fisiol. Vegetal., 5:307-439, 1949.
194. Von Fraenkel, P. J.: U. S. Nav. Med. Bull., 49:280-288, 1949.
195. Wade, A.: Atmospheric pollution; the present position and the outlook for the future. J. Roy. San. Inst., 69:699-705, (Nov.) 1949.
196. Walton, C. H. A.: Respiratory allergy due to fungi. Canad. M. A. J., 60: 275-6, (Mar.) 1949.
197. Walzer, Abraham: Evaluation of electrophoretic method of skin testing. J. Allergy, 20:77, (Jan.) 1949.
198. Warren, S., and Dixon, F. J.: Antigen tracer studies in anaphylactic shock. J.A.M.A., 139:402 (Feb. 5) 1949.
199. Weil, A. J., and Rose, E.: Separation by means of ammonium salts of the antibody-antigen reaction from the response of the smooth muscle. Ann. Allergy, 7:108-113, 1949.
200. William, H. L.: Phylogenetic concept of allergy. Proc. Staff. Meet., Mayo Clin., 24:516-524, (Sept. 28) 1949.
201. Williams, E. O., and Williams, G. E. O.: Natural history of asthma. J.A.M.A., 142:762, (Mar. 11) 1949.
202. Wittich, F. W.: A clinical evaluation of Orthoxine in the treatment of allergic diseases. Ann. Allergy, 6:646-666, (Nov.) 1948.
203. Wittich, F. W.: Diagnosis and treatment of common forms of respiratory allergy. Minnesota Med., 32:702-8, (July) 1949.
204. Wittich, F. W.: Importance of allergy disease in medicine. Delaware State M. J., 21:43-50, (Mar.) 1949.
205. Wittich, F. W.: The importance of mold spores in ophthalmic and otorhinolaryngologic allergy. Alergia, 2:85-91, (Nov.-Feb.) 1948, 1949.
206. Wodehouse, Roger P.: The origin of patterns of allergic sensitization. Ann. Allergy, 7:172-185, 1949.
207. Wolf, A. F.: The status of allergy in relation to medical practice. South. M. J., 42:808-813, (Sept.) 1949.
208. Woods, A. C.: The diagnosis and treatment of ocular allergy. Am. J. Ophth., 32:1457-78, (Nov.) 1949.
209. Wright, J. B.: Histamine antagonists: indole and carbazole and derivatives. J. Am. Chem. Soc., 71:1028-30, (Mar.) 1949.
210. Yonkman, F. F., and Mohr, F. L.: An approach to the problem of epinephrine-fastness. Ann. Allergy, 7:60, (Jan.-Feb.) 1949.

211. Zeller, Michael: Nasal Pyribenzamine for relief of hay fever. Ann. Allergy, 7:103-105, 1949.
212. Zolov, Benjamin: Benadryl: intravenous use in allergy. Ann. Allergy, 7:254-258, 1949.
213. Zolov, B.: Clinical evaluation of Pyrrolazote and Orthoxine in allergic diseases. J. Maine M. A., 40:105-107, (May) 1949.

BOOKS

214. Abramson, Harold A.: Psychodynamics and the Allergic Patient. St. Paul: Bruce Publishing Co., 1949.
215. Brown, G. T.: Pollen Slide Studies. Springfield: Charles C Thomas, 1949.
216. Conn, Howard F.: Current Therapy. Philadelphia: W. C. Saunders Co., 1949.
217. Hansel, French K.: Allergy in Relation to Otolaryngology. St. Paul: Bruce Publishing Co., 1949.
218. Kallos, Paul. Progress in Allergy. New York: Interscience Publishing, Inc., 1949.
219. Swartz: Allergy—What It Is and What To Do About It. 1949.
220. Tuft, Louis: Clinical Allergy. Philadelphia: Lea & Febiger, 1949.
221. Vallery-Radot, Pasteur: Allergie. Paris: L'Expansion Scientifique Francaise, 1949.

EFFECTIVENESS OF A COMBINATION OF AN ANTIHISTADINE DECARBOXYLASE AND AN ANTIHISTAMINE

(Continued from Page 14)

Of the total of thirty-seven patients treated in this study, only two patients complained of drowsiness. This remarkably low incidence of side effects is attributed to the use of the combination of d-catechin and dimethylaminopropylphenothiazine.

REFERENCES

1. Bain, W. A.; Broadbent, J. L., and Warin, R. P.: Comparison of Anthisan (mepyramine maleate) and Phenergan as histamine antagonists. Lancet, 2:47, (July 9) 1949.
2. Halpern, B. N.: Recent advances in the domain of the antihistamine substances: the phenothiazine derivatives. Bull. New York Acad. Med., 25:323, (May) 1949.
3. Martin, Gustav J.; Graff, M.; Brendel, R., and Beiler, J. M.: Effects of vitamin P compounds on the action of histidine decarboxylase. Arch. Biochem., 21:177, 1949.
4. Moss, J. N.; Beiler, J. M., and Martin, G. J.: The inhibition of anaphylaxis in guinea pigs by d-catechin. Science, (in press).
5. Shulman, Maurice D.: Phenergan, preliminary report of clinical effectiveness. Ann. Allergy, 7:506, 1949.
6. Waldbott, G. L., and Gadbaw, J. J.: An evaluation of antihistaminics. J. Michigan M. Soc., 48:724, 1949.

Community Hospital, 10th and Carpenter Streets.

News Items

SOUTHWEST ALLERGY FORUM

The Southwest Allergy Forum will meet April 8, 9, and 10 at the Plaza Hotel in San Antonio. Registration will start on Sunday, April 8, and a cocktail party will be held at 5:30 p.m. Dr. Walter L. Rucks of Memphis, Tennessee, is the acting president for this meeting, with Dr. J. W. H. Rouse of San Antonio, Texas, as the president-elect. The program is as follows:

APRIL 9

Morning

9:30 President's address: Concepts of Pediatric Allergy
Dr. Walter L. Rucks, Memphis, Tennessee

9:45 Asthma Associated with Hyperthyroidism
Dr. Saul Grossman, Corpus Christi, Texas
The Nonspecific Use of Thyroid Substance
Dr. Lawrence J. Halpin, Cedar Rapids, Iowa

10:15 Neuromuscular Pain on an Allergic Basis
Dr. J. Bartow Talley, Temple, Texas

10:45 The Factor of Gastrointestinal Disease and Dysfunction in Allergy
Dr. Julia Baker, Mexico City, Mexico

11:30 Is There a Physiologic Basis for Allergy?
Dr. J. Harvey Black, Dallas, Texas

12:15 Luncheon for members, Plaza Hotel; luncheon for the ladies, Menger Hotel

Afternoon

1:30 Intravenous Therapy of Allergic Disease
Dr. John W. Winter, San Antonio, Texas (by invitation)
Discussion, Dr. Bernard Fein, San Antonio, Texas

2:00 Psychosomatic Background in Allergy
Drs. Hyman Miller and Dorothy Baruch, Beverly Hills, California

3:15 Roundtable on ACTH and Cortisone
Dr. Cecil Kohn, Kansas City, Moderator

4:45 Business meeting

6:00 Cocktail party, Cos House, Texas Pharmacal Co.

7:30 Dinner in honor of Dr. I. S. Kahn
Eulogy by Dr. J. Harvey Black, Dallas, Texas
La Villita, "A Night in Old Mexico"

APRIL 10

Morning

9:00 President's address: Debunking the Antihistamines
Dr. J. W. H. Rouse, San Antonio, Texas

9:30 Is There an Allergy to Bacteria?
Dr. Albert M. Tocker, Dallas, Texas

10:00 Treatment of Allergic Headache
Dr. Henry D. Ogden, New Orleans, Louisiana

10:45 The Cytology of Allergic Responses, Experimental
Drs. C. M. Pomerot and J. M. Rose, Galveston, Texas

11:30 Clinical Laboratory Procedures Useful in the Management of Allergic Patients
Dr. L. O. Dutton, El Paso, Texas

12:15 Luncheon, Plaza Hotel

1:45 Roundtable on the Problems of Asthma
Dr. Allan Cazort, Pipe Creek, Arkansas

1951 ESSAY CONTEST

The Eleventh Annual Essay Contest of the Mississippi Valley Medical Society will be held in 1951. The Society will offer a cash prize of $100, a gold medal, and a certificate of award for the best unpublished essay on any subject of general medical interest (including medical economics and education) and practical value to the general practitioner of medicine. Certificates of merit may also be granted to the physicians whose essays are rated second and third best. Contestants must be members of the American Medical Association who are residents and citizens of the United States. The winner will be invited to present his contribution before the Sixteenth Annual Meeting of the Mississippi Valley Medical Society to be held in Peoria, Illinois, September 19, 20, 21, 1951, the Society reserving the right to first publish the essay in its official publication—*The Mississippi Valley Medical Journal.* All contributions shall be typewritten in English in manuscript form, submitted in five copies, not to exceed 5000 words, and must be received not later than May 1, 1951.

Further details may be secured from Harold Swanberg, M.D., Secretary, Mississippi Valley Medical Society, 209 W.C.U. Building, Quincy, Illinois.

AMERICAN PSYCHOSOMATIC SOCIETY

The Eighth Annual Meeting of the American Psychosomatic Society will take place at Chalfonte-Haddon Hall, Atlantic City, New Jersey, Saturday, April 28, 1951. Both the morning and afternoon sessions will be composed of papers of a varied nature, rather than confining the papers to one or two panel topics. The customary cocktail party will close the 1951 meeting.

The registration fee for nonmembers of the Society is $2.00; there will be no fee for members. The program of the meeting, as well as a hotel reservation card, will be ready for distribution from the Society office after March 15, and will be available upon request to Sydney G. Margolin, M.D., Secretary-Treasurer, American Psychosomatic Society, 714 Madison Avenue, New York 21, N. Y.

NEW YORK STATE JOURNAL OF MEDICINE

ANNALS OF ALLERGY congratulates the *New York State Journal of Medicine* on its Golden Anniversary Issue, which recently appeared decked in a special gold-colored cover. The Journal, official publication of the Medical Society of the State of New York, commemorated fifty years of continuous publication with its January 1 issue. Doctors prominent in many fields of medicine have contributed articles describing the advances made during the first half of the Twentieth Century. The Journal goes regularly to the 23,000 members of the state society and to a number of subscribers in all parts of the world. We hope that most of our A.C.A. members noticed our half-page advertisement for the Instructional Course and the Seventh Annual Congress, which was in part responsible for the fine attendance in Chicago.

BRAZILIAN INSTITUTE FOR THE HISTORY OF MEDICINE

At a meeting of the Brazilian Institute for the History of Medicine at the General Polyclinic of Rio de Janeiro, September 27, the following papers were presented: "The Sanitary Organization in the San Martinian Campaigns" by Prof. Francisco Cignoli; "Two Centennials in the History of the Sciences" by Prof. Antonio Carlos Vilanova; "Memorial of Charles Richet, in the Centennial of His Birth" by Dr. Ordival Gomes; and "The Saints Cosmian and Damian in the History of Medicine" by Dr. Ivolino de Vasconcellos.

BOOK REVIEWS

METHODS IN MEDICAL RESEARCH, VOLUME III. Ralph W. Gerard, Editor-in-Chief, and four editors. 312 pages, with numerous figures. Price $7.00. Chicago: Year Book Publishers, Inc., 1950.

This eagerly anticipated Volume III has just appeared and is most welcome. This series of volumes devoted to methods and techniques in medical research has supplied a need for those who are devoting time to research problems of a high order. It is a valuable addition to a collection where there is an appraisal and discussion of the various methods proposed for the solution of some experimental problem. It includes adequate description of techniques which have been modified and improved by continued use. This series will gradually increase in value as a widening field is steadily encompassed.

Each volume is divided into three to five principal, self-contained sections which represent one of the broad fields of medical research, such as biochemistry, physiology and pharmacology, microbiology and immunology, and biophysics including radiobiology. In each volume, the governing boards have selected experts to act as associate editors for their assigned topic for the year.

Volume IV is in active preparation and will be available in the winter of 1950-51.

The contributors and reviewers are to be congratulated on compiling these volumes, for making available greater and easier productivity in experimentation.

ANTIHISTAMINES—INDUSTRY AND PRODUCT SURVEY. By Nathan Wishnefsky. 57 pages, with chemical diagrams. Paper bound. Price $5.00. New York: Chemonomics, Inc., 1950.

This monograph represents a fairly complete, up-to-date compilation of the evaluation of antihistamines made in an industry and product survey. It describes the background, development, clinical evaluation, and laboratory and clinical comparisons of the modern antihistamines used in the United States. It includes their chemical structure, chemical names, and trademark names. It brings together in one volume the important published knowledge of the antihistamines, including the theoretical and practical considerations of allergy and the common cold.

The book gives some interesting statistics as to the amount in millions of the annual sales of the antihistamines. A detailed account is given of the report of the Federal Trade Commission concerning the sale of the antihistamines exploited for the treatment of colds and sold over the counter. There is a bibliography of over 250 references.

PHYSIOLOGY OF THE EYE. Clinical Application. By Francis Heed Adler, Professor of Ophthalmology, School of Medicine, University of Pennsylvania; Consulting Surgeon, Wills Hospital, Philadelphia. 709 pages, 319 illustrations including 2 in color. Price $12.00. St. Louis: C. V. Mosby Co., 1950.

Such rapid progress has been made in the past twenty years on the subject of the physiology of the eye that an entirely new book has been written by the author. The basic physiology of the material has received an entirely fresh treatment. Just as the application of physiology to the study of disease has been so prolific in many fields of medicine and surgery, it is necessary also to have a knowledge of the function of the various parts of the eye to understand ocular disorders. It is necessary for the ophthalmologist to know how the eye normally functions before he can treat its diseases. Rational treatment of glaucoma should be based on a

knowledge of the formation and elimination of the aqueous humor, the permeability characteristics of the cornea, and the hemodynamics of the ocular circulation. The medical and surgical approach to strabismus should be through a comprehension of the neuromuscular mechanisms which normally maintain the two eyes in alignment.

There are twenty-two chapters covering the findings of the physiology of the eye which have been gleaned from the experimental laboratory, and the book applies these facts clinically. There is an extensive reference list at the end of each chapter, and no ophthalmologist should be without this book. The publishers are to be congratulated for their usual excellent paper stock and illustrations.

BACTERIAL POLYSACCHARIDES. By Martin Burger. 272 pages, 48 tables. Price $6.00. Springfield, Ill.: Charles C Thomas, 1950.

This is a concise compilation of data on methods of isolating carbohydrate bacterial substances. This field is becoming more important from the viewpoint of public health to physicians, chemists, bacteriologists, hematologists, serologists, allergists, enzymologists, veterinarians, dentists, and immunologists. It gives very valuable data on the use of these carbohydrates as diagnostic reagents. The book covers comprehensively those polysaccharide substances which are more or less directly related to infection and immunity. Much of the material deals with carbohydrate substances which reside in the pathogenic bacteria and are recognized as the factors responsible for certain immune reactions. There is an authors' index as well as an extensive bibliography following each chapter.

There are fifteen chapters with an appendix describing in detail the techniques for isolation, purification, and extraction. Finally, as is usual with Thomas books, careful attention is given to all details of manufacture and design. The cover is of DuPont fabrikoid.

NEWER CONCEPTS OF INFLAMMATION. By Valy Menkin, Associate Professor and Head of Experimental Pathology, Temple University School of Medicine, Philadelphia. 152 pages, 67 figures. Price $3.50. Springfield, Ill.: Charles C Thomas, 1950.

This monograph is one of the American Lecture Series. Ever since the original monograph of Professor Adami half a century ago there has been need of a concise monograph on the subject. Reviewed here are the studies which are focused on an attempt to understand the basic mechanisms involved in the development of this elementary immunological response. This subject is of exceeding importance to dentists and practical physicians. It contains much new information developed in the past ten years on the subject. The author emphasizes the biochemistry of injured cells, since many of the biological attributes of an acute inflammation are referrable to the liberation by injured cells of biochemical units, in turn liberated by the injured cell.

There are five chapters dealing with the problem of increased capillary permeability in inflammation and the role of the hydrogen ion concentration in the development of the reaction, the role of inflammation in immunity, phagocytosis, chemical factors in inflammation, diabetes in inflammation, and the causes of fever and leukopenia in inflammatory conditions.

There are 67 excellent figures, most of them photomicrographs, which are very clear. The cover is Roxite vellum, two-tone black. The volume makes a handy desk reference.